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(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.

- 5 60/298,173 filed on June 14, 2001, U.S. Provisional Application No. 60/311,686
filed on August 10, 2001, and U.S. Provisional Application No. 60/316,995, filed on
September 4, 2001. The entire teachings of the above applications are incorporated
herein by reference.

10 GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grant CA-0974823 from
the National Cancer Institute. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

- 15 The N-terminal tails of core histones are covalently modified by post-
translational modifications, including acetylation and phosphorylation. Evidence
suggests that these covalent modifications play important roles in several biological
activities involving chromatin, *e.g.*, transcription and replication. Histone
deacetylases (HDACs) catalyze the removal of the acetyl group from the lysine
20 residues in the N-terminal tails of nucleosomal core histones resulting in a more
compact chromatin structure, a configuration that is generally associated with
repression of transcription.

- Five proteins and/or open reading frames in yeast (RPD3, HDA1, HOS1,
HOS2 and HOS3) that share significant homology in the catalytic domain have been
25 identified as HDACs based upon their sequence homology to human HDAC1. To
date, eight HDACs have been identified in mammalian cells, and classified into two
classes based on their structure and similarity to yeast RPD3 or HDA1 proteins.
Recently, Sir2 family proteins that are structurally unrelated to the five proteins
aforementioned have been identified as NAD-dependent HDACs. Class I HDACs
30 are the yeast RPD3 homologs HDAC1, 2, 3, and 8, and are composed primarily of a
catalytic domain. Class II HDACs are the yeast HDA1 homologs HDAC4, 5, 6; and

7. HDAC4, 5, and 7 contain a long non-catalytic N-terminal end and a C-terminal HDAC catalytic domain while HDAC6 has two HDAC catalytic domains.

It has also been determined that histone deacetylases can be sensitive to small molecules, including trichostatin A (TSA), trapoxin, and butyrate. For example, the yeast RPD3 and HDA1 and mammalian HDAC1, 2, 3, 4, 5, 6, 7 and 8 are sensitive to inhibition by trichostatin A (TSA). The Sir2 family HDACs, yeast HOS3 and *Drosophila melanogaster* dHDAC6, however, appear to be relatively insensitive to TSA. A class of hybrid bipolar compounds, such as suberoylanilide hydroxamic acid (SAHA) have also been shown to inhibit histone deacetylases and induce terminal differentiation and/or apoptosis in various transformed cells. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, as well as U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, the entire content of all of which are hereby incorporated by reference.

The identification of the mechanisms by which histones are deacetylated, and the characterization of histone deacetylase function would be of great benefit in understanding how gene transcription is controlled, how the cell cycle is regulated, and how cells are signaled to undergo terminal differentiation and/or apoptosis. Elucidation of such mechanisms can lead to improved therapeutics for many diseases, in particular those characterized by cell proliferation or a lack of cell differentiation or apoptosis, for example, cancer.

SUMMARY OF THE INVENTION

The present invention relates to isolated or recombinant histone deacetylase polypeptides, and isolated histone deacetylase nucleic acid molecules encoding those polypeptides, as well as vectors and cells containing those isolated nucleic acid molecules.

In one aspect of the invention, the isolated or recombinant histone deacetylase polypeptide is selected from a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and b) a polypeptide having at least 60% sequence identity with any one

of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In one embodiment, the isolated or recombinant histone deacetylase polypeptide consists of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In another embodiment, the isolated or recombinant histone deacetylase polypeptide is mammalian; preferably, the isolated or recombinant histone deacetylase polypeptide is human.

In another aspect, the invention features an isolated nucleic acid molecule selected from a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; e) a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or f) a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof. In one embodiment, the isolated nucleic acid molecule consists of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the isolated nucleic acid molecule is mammalian; preferably, the isolated nucleic acid molecule is human.

In other aspects, the invention features a vector comprising the isolated histone deacetylase nucleic acid molecule described above, a cell comprising the vector, and a cell comprising the isolated histone deacetylase nucleic acid molecule described above.

In another aspect, the invention features a purified antibody that selectively binds a histone deacetylase polypeptide described above.

In yet another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) contacting the nucleic acid molecule with a candidate compound under conditions suitable for expression; and
5 b) assessing the level of expression of the nucleic acid molecule. A candidate compound that increases or decreases expression of the nucleic acid molecule relative to a control is a compound that modulates expression of the nucleic acid molecule. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

10 The invention also features a method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, for example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer and myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid
15 metaplasia, and chronic myelogenous leukemia in an individual, comprising administering a compound identified by the above method.

In still another aspect, the invention features a method of identifying a compound that modulates the enzymatic activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the
20 polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and b) assessing the activity level of the polypeptide. A candidate compound that increases or decreases the activity level of the polypeptide relative to a control is a compound that modulates the enzymatic activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
25 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
30 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates the transcriptional repression activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the polypeptide with a candidate compound under conditions suitable for a
5 transcriptional repression reaction; and b) assessing the transcriptional repression activity level of the polypeptide. A candidate compound that increases or decreases the transcriptional repression activity level of the polypeptide relative to a control is a compound that modulates the transcriptional repression activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
10 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
15 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) providing a nucleic acid molecule
20 comprising a promoter region of the histone deacetylase nucleic acid molecule described above, or part of such a promoter region, operably linked to a reporter gene; b) contacting the nucleic acid molecule or with a candidate compound; and c) assessing the level of the reporter gene. A candidate compound that increases or decreases expression of the reporter gene relative to a control is a compound that
25 modulates expression of the histone deacetylase nucleic acid molecule described above. In one embodiment, the method is carried out in a cell.

In still another aspect, the invention features a method of identifying a polypeptide that interacts with a histone deacetylase polypeptide described above in a yeast two-hybrid system. The method comprises the steps of a) providing a first
30 nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and the histone deacetylase polypeptide described above; b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription

activation domain and a nucleic acid encoding a test polypeptide; c) contacting the first nucleic acid vector with the second nucleic acid vector in a yeast two-hybrid system; and d) assessing transcriptional activation in the yeast two-hybrid system. An increase in transcriptional activation relative to a control indicates that the test
5 polypeptide is a polypeptide that interacts with the histone deacetylase polypeptide described above.

The invention also features a pharmaceutical composition comprising a histone deacetylase polypeptide described above.

In addition, the present invention features a method of diagnosing a cell
10 proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject. The method comprises the steps of a) obtaining a sample from the subject; and b) assessing the level of activity or expression of the histone deacetylase polypeptide described above or the level of the nucleic acid molecule described above in the sample. If the level is increased relative to a control, then the subject
15 has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and if the level is decreased relative to a control, then the subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In one embodiment, the polypeptide level is assayed using immunohistochemistry techniques. In another
20 embodiment, the nucleic acid molecule level is assayed using *in situ* hybridization techniques.

Compounds and/or polypeptides identified in the above-described screening methods are also part of the present invention.

25 DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic representation of the order in which FIGS. 1A-1O should be viewed.

FIGS. 1A-1C show the cDNA sequence of *HDAC9* (SEQ ID NO: 1). The arrows and numbers in the *HDAC9* sequence indicate exons. The boxed portion of
30 the sequence indicates the HDAC domain.

FIGS. 1D-1G show the cDNA sequence of *HDAC9a* (SEQ ID NO: 3). The arrows and numbers in the *HDAC9a* sequence indicate exons. The boxed portion of the sequence indicates the HDAC domain.

FIGS. 1H-1I show the cDNA sequence of *HDRP*(Δ NLS) (SEQ ID NO:9).

5 FIGS. 1J-1L show the cDNA sequence of *HDAC9*(Δ NLS) (SEQ ID NO:5).

FIGS. 1M-1O show the cDNA sequence of *HDAC9a*(Δ NLS) (SEQ ID NO:7).

FIG. 2 is a schematic representation of the order in which FIGS. 2A-2E should be viewed.

10 FIG. 2A shows the amino acid sequence of HDAC9 (SEQ ID NO: 2).

FIG. 2B shows the amino acid sequence of HDAC9a (SEQ ID NO: 4).

FIG. 2C shows the amino acid sequence of HDAC9(Δ NLS) (SEQ ID NO: 6).

FIG. 2D shows the amino acid sequence of HDAC9a(Δ NLS) (SEQ ID NO: 8).

15 FIG. 2E shows the amino acid sequence of and HDRP(Δ NLS) (SEQ ID NO: 10).

FIG. 3 is a schematic representation of the order in which FIGS. 3A-3C should be viewed.

20 FIGS. 3A-3C show an amino acid sequence alignment of HDRP (SEQ ID NO: 11), HDAC9 (SEQ ID NO: 2), HDAC9a (SEQ ID NO: 4), and HDAC4 (SEQ ID NO: 12) polypeptides. Amino acid sequences of HDAC9 (GenBank Accession: AY032737; SEQ ID NO: 2) and HDAC9a (GenBank Accession: AY032738; SEQ ID NO: 4) are aligned with HDRP (GenBank Accession: BAA34464; SEQ ID NO: 11) and HDAC4 (GenBank Accession: NP_006028; SEQ ID NO: 12). The identical
25 residues in all proteins are boxed with solid lines. The similar residues are boxed with dotted lines.

FIG. 4 shows a schematic representation of the human *HDAC9* gene structure. The striped boxes represent exons present in isoforms HDRP, HDAC9a, and HDAC9. The lines represent introns. Broken lines are used for larger introns
30 (with size in base pair on top). The 5' untranslated region cDNA and coding region cDNA are represented here. Exons 1-12 encode a non-catalytic domain of the

polypeptides, and exons 14-21 encode the histone deacetylase catalytic domain of the polypeptides, which provide the polypeptides with deacetylase activity.

FIG. 5 is a schematic representation of the order in which FIGS. 5A-5D should be viewed.

5 FIGS. 5A-5D show the nucleic acid sequence of *HDAC9*, containing all exons expressed in the various isoforms of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* of the present invention (SEQ ID NO:13).

FIG. 6A is a scanned image of a multiple human tissue Northern blot that was probed to determine mRNA expression of *HDAC9* using a cDNA probe that
10 recognizes both *HDAC9* and *HDAC9a*. The tissues examined are lane 1, heart; lane 2, brain; lane 3, placenta; lane 4, lung; lane 5, liver; lane 6, skeletal muscle; lane 7, kidney; and lane 8, pancreas. Positions of the RNA size marker in kilobases (kb) are indicated to the left of the blot.

FIG. 6B is a scanned image of an electrophoretic gel showing the results of
15 RT-PCR analyses of mRNA from the same tissues as examined in the Northern blot of FIG. 6A to determine the distribution of *HDAC9* and *HDAC9a* mRNA among these tissues. PCR products were resolved by agarose gel electrophoresis and visualized by ethidium bromide under UV light. A 1-kb DNA ladder was run on both sides of the gel with the size (in kb) indicated on the left. On the right side, the
20 expected products for *HDAC9* and *HDAC9a* are indicated as 9 and 9a, respectively.

FIG. 7 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, HDAC9-FLAG, and HDAC9a-FLAG transfected 293T cells, as measured in fluorescence units using *FLUOR DE LYS*[™] as a substrate in the presence or absence of 1 μM TSA. Results
25 are shown as the mean of three independent assays. The inset is a scanned image of an anti-FLAG Western blot showing the amount of proteins used in the assay. V, Vector control; 9, HDAC9-FLAG; and 9a, HDAC9a-FLAG.

FIG. 8 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, and HDAC9a-FLAG
30 (treated with 2 μM SAHA or left untreated) transfected 293T cells, as measured by ³H-acetic acid released from ³H-histones in the presence or absence of 2 μM SAHA.

Vector control; HDAC9a, HDAC9a-FLAG; and HDAC9a+, HDAC9a-FLAG + SAHA.

FIG. 9A shows a scanned image of a Western blot of 293T whole cell lysate and anti-FLAG immunoprecipitates from 293T cells transfected with vector,

5 HDAC9-FLAG or HDAC9a-FLAG using antibodies against MEF2 and FLAG. Top panel, anti-MEF2 Western; bottom panel, anti-FLAG Western. L, 293T whole cell lysate; V, vector control IP; 9, HDAC9-FLAG IP; 9a, HDAC9a-FLAG IP.

FIG. 9B is a graph showing the transcription level of p3XMEF2-*Luc* in the presence or absence of pcDNA3 empty vector (-), pCMV-MEF2C, and/or a vector
10 encoding pFLAG-HDAC9 or pFLAG-HDAC9a. p3XMEF2-*Luc* (100 ng) and pRL-TK (5 ng) were transfected into 293T cells with pcDNA3 empty vector (-) or with pCMV-MEF2C (100 ng) (+) along with the indicated amount of pFLAG-HDAC9 or pFLAG-HDAC9a. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The firefly luciferase activity was first normalized to
15 the co-transfected Renilla luciferase activity and the value for MEF2C alone was then set as 1. Results are shown as the mean of three independent transfections +/- standard deviation.

FIG. 10 shows a schematic representation of the HDAC domains of human non-Sir2 family HDACs and HDRP. The boxes represent histone deacetylase
20 (HDAC) domains.

FIG. 11 is a schematic representation of the order in which FIGS. 11A-11F should be viewed.

FIGS. 11A-11F show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9 (VR1) (SEQ ID NO: 14). Lowercase letters are vector backbone,
25 uppercase letters are HDAC9 sequence. "Acc" was added at the beginning of the HDAC9 sequence for translation initiation.

FIG. 12 is a schematic representation of the order in which FIGS. 12-1 through 12-66 should be viewed.

FIGS. 12-1 through 12-66 show the nucleotide sequence of the vector
30 pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 14).

FIG. 13 is a schematic representation of the order in which FIGS. 13A-13E should be viewed.

FIGS. 13A-13E show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2) (SEQ ID NO: 15). Lowercase letters are vector backbone, .
5 uppercase letters are HDAC9a sequence. "Acc" was added at the beginning of the HDAC9a sequence for translation initiation.

FIG. 14 is a schematic representation of the order in which FIGS. 14-1 through 14-61 should be viewed.

FIGS. 14-1 through 14-61 show the nucleotide sequence of the vector
10 pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 15).

DETAILED DESCRIPTION OF THE INVENTION

A protein designated HDRP (See Zhou *et al.*, Proc. Natl. Acad. Sci. USA,
15 97:1056-1061 (2000)) (also called MITR (See Sparrow *et al.*, EMBO J. 18:5085-5098(1999); Zhang *et al.*, J. Biol. Chem., 276:35-39 (2001); and Zhang *et al.*, Proc. Natl. Acad. Sci. USA, 98:7354-7359 (2001)) that is 50% identical to the N-terminal domains of histone deacetylase 4 (HDAC4) and histone deacetylase 5 (HDAC5) was recently identified. The cloning and characterization of a novel histone deacetylase,
20 *HDAC9*, of which HDRP is an alternatively spliced isoform is described herein. The cDNA sequence of *HDAC9* is shown in FIGS. 1A-1C (SEQ ID NO: 1), and the HDAC9 amino acid sequence is shown in FIG. 2A (SEQ ID NO: 2). In addition to cloning *HDAC9*, other alternatively spliced isoforms of HDAC9, designated as HDAC9a (a polypeptide that is 132 amino acids shorter at the C-terminal end than
25 HDAC9), and isoforms of HDAC9, HDAC9a, and HDRP polypeptides that lack the nuclear localization signal (NLS) in the N-terminal non-catalytic end of HDAC9, termed HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS), respectively were also identified. The cDNA sequence of *HDAC9a* is shown in FIGS. 1D-1G (SEQ ID NO: 3), and the HDAC9a amino acid sequence is shown in FIG. 2B (SEQ ID
30 NO: 4). The cDNA sequence of *HDAC9* lacking amino acids encoding an NLS (*HDAC9*(Δ NLS)) is shown in FIGS. 1J-1L (SEQ ID NO: 5), and the HDAC9 lacking an NLS amino acid sequence is shown in FIG. 2C (SEQ ID NO: 6). The cDNA

sequence of *HDAC9a* encoding a polypeptide lacking an NLS (*HDAC9a*(Δ NLS)) is shown in FIGS. 1M-1O (SEQ ID NO: 7), and the *HDAC9a* lacking an NLS amino acid sequence is shown in FIG. 2D (SEQ ID NO: 8). The cDNA sequence of *HDRP* encoding a polypeptide lacking an NLS (*HDRP*(Δ NLS)) is shown in FIGS. 1H-1I (SEQ ID NO: 9), and the *HDRP* lacking an NLS amino acid sequence is shown in FIG. 2E (SEQ ID NO: 10).

POLYPEPTIDES OF THE INVENTION

The present invention features isolated or recombinant *HDAC9* polypeptides, *HDAC9a* polypeptides, *HDAC9*(Δ NLS) polypeptides, *HDAC9a*(Δ NLS) polypeptides, and *HDRP*(Δ NLS) polypeptides, and fragments, derivatives, and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (e.g., other variants). As used herein, the term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides, and proteins are included within the definition of a polypeptide.

As used herein, a polypeptide is said to be "isolated," "substantially pure," or "substantially pure and isolated" when it is substantially free of cellular material, when it is isolated from recombinant or non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. Typically, the *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) polypeptide is isolated, substantially pure, or substantially pure and isolated when it has a relative increased concentration or activity of *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS), in comparison to total *HDAC* concentration or activity. Preferably the increased activity or concentration of the *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) is at least 2-fold, more preferably, at least 5-fold, and most preferably, at least 10 fold, in comparison to total *HDAC* concentration or activity. In addition, a polypeptide can be joined to another polypeptide with which it is not normally associated in a cell (e.g., in a "fusion protein") and still be "isolated," "substantially pure," or "substantially pure and isolated." An isolated, substantially pure, or substantially pure and isolated polypeptide may be obtained, for example, using affinity

purification techniques described herein, as well as other techniques described herein and known to those skilled in the art.

By a "histone deacetylase polypeptide" is meant a polypeptide having histone deacetylase activity, transcription repression activity, and/or the ability to deacetylate other substrates, for example, transcription factors, including p53, CoRest, E2F, GATA-1, TFIIe, and TFIIIF that normally have a nuclear or cytoplasmic location in a cell. A histone deacetylase polypeptide is also a polypeptide whose activity can be inhibited by molecules having HDAC inhibitory activity. These molecules fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids(e.g. SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, Bioessays 17, 423-430 (1995), Saito *et al.*, PNAS USA 96, 4592-4597, (1999), Furumai *et al.*, PNAS USA 98 (1), 87-92 (2001), Komatsu *et al.*, Cancer Res. 61(11), 4459-4466 (2001), Su *et al.*, Cancer Res. 60, 3137-3142 (2000), Lee *et al.*, Cancer Res. 61(3), 931-934 and Suzuki *et al.* J. Med. Chem. 42(15), 3001-3003 (1999) the entire content of all of which are hereby incorporated by reference. Examples of such histone deacetylase polypeptides include HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), HDRP(Δ NLS); a substantially pure polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and a polypeptide having preferably at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, as determined using the BLAST program and parameters described herein.

In one embodiment, the histone deacetylase polypeptide has histone deacetylase activity, transcription repression activity, the ability to deacetylate substrates, or is inhibited by trichostatin A or a hybrid polar compound such as

SAHA. In another embodiment, the HDAC9(Δ NLS) polypeptide has any two of the above biological activities. In still another embodiment, the HDAC9(Δ NLS) polypeptide has any three of the above biological activities. In yet another embodiment, the HDAC9(Δ NLS) polypeptide has all of the above biological activities.

- 5 An HDAC9 polypeptide is a histone deacetylase polypeptide as described above. An HDAC9 polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 2, as determined using the BLAST program and parameters described herein.
- 10 An HDAC9 polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25 and/or 26, and that does not comprise the amino acids encoded by exon 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1A-1C, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9 polypeptide comprises the sequence of SEQ ID NO: 2. More preferably, an HDAC9 polypeptide consists of
- 15 the sequence of SEQ ID NO: 2. An HDAC polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1.

- An HDAC9a polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a polypeptide preferably has at least 60%, more preferably, 70%,
- 20 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 4, as determined using the BLAST program and parameters described herein. An HDAC9a polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1D-
- 25 1G, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9a polypeptide comprises the sequence of SEQ ID NO: 4. More preferably, an HDAC9a polypeptide consists of the sequence of SEQ ID NO: 4. An HDAC9a polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 3.

- 30 An HDAC9(Δ NLS) is a histone deacetylase polypeptide as described above. An HDAC9(Δ NLS) polypeptide does not comprise a nuclear localization signal (NLS). An HDAC9(Δ NLS) polypeptide preferably has at least 60%, more

preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 6, as determined using the BLAST program and parameters described herein. An HDAC9(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25, and/or 26, and that does not
5 comprise the amino acids encoded by exons 7 or 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1J-1L, and FIGS. 5A-5D. Preferably, an HDAC9(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 6. More preferably, an HDAC9(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 6. An HDAC9(Δ NLS) polypeptide is also a polypeptide comprising the amino acid
10 sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 5.

An HDAC9a(Δ NLS) polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDAC9a(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence
15 identity to SEQ ID NO: 8, as determined using the BLAST program and parameters described herein. An HDAC9a(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 7, 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1M-1O, and FIGS. 5A-5D. Preferably, an
20 HDAC9a(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 8. More preferably, an HDAC9a(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 8. An HDAC9a(Δ NLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 7.

An HDRP(Δ NLS) polypeptide is a histone deacetylase polypeptide as
25 described above. An HDRP(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDRP(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 10, as determined using the BLAST program and parameters described herein. An HDRP(Δ NLS) polypeptide is also a polypeptide that does not comprise
30 the amino acids encoded by exons 7 or 13-26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1H-1I and FIGS. 5A-5D. Preferably, an HDRP(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 10. More preferably, an

HDRP(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 10. An HDRP(Δ NLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 9.

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, (*e.g.*, a complement of any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 or a portion of any one of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9).

The polypeptides of the invention also encompass fragments and sequence variants. Variants include a substantially homologous polypeptide encoded by the

- same genetic locus in an organism, *i.e.*, an allelic variant, as well as other variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences encoding any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 10 Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.
- 15

- As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 60-65%, typically at least about 70-75%, more typically at least about 80-85%, and most typically greater than about 90-95% or more homologous or identical. A substantially identical or homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a portion thereof, under stringent conditions as more particularly described herein, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or portion thereof, under stringent conditions as more particularly described herein.
- 20
- 25

- The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). In
- 30

certain embodiments, the length of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) amino acid or nucleotide sequence aligned for comparison purposes is at least 30%, preferably, at least 40%, more preferably, at least 60%, and even more preferably, at least 70%, 80%, 90%, or 100% of the length of the reference sequence, for example, those sequences provided in FIGS. 1A-1O and 2A-2E. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993). Such an algorithm is incorporated into the BLASTN and BLASTX programs (version 2.2) as described in Schaffer *et al.*, Nucleic Acids Res., 29:2994-3005 (2001). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>, as available on August 10, 2001. In one embodiment, the database searched is a non-redundant (NR) database, and parameters for sequence comparison can be set at: no filters; Expect value of 10; Word Size of 3; the Matrix is BLOSUM62; and Gap Costs have an Existence of 11 and an Extension of 1.

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0), which is part of the GCG (Accelrys) sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, Comput. Appl. Biosci., 10: 3-5 (1994); and FASTA described in Pearson and Lipman, Proc. Natl. Acad. Sci USA, 85: 2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.accelrys.com>, as available on August 31, 2001) using either a Blossom 63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent

identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.cgc.com>), using a gap weight of 50 and a length weight of 3.

- The invention also encompasses HDAC9, HDAC9a, HDAC9(Δ NLS),
- 5 HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions
- 10 are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu;
- 15 substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, Science 247: 1306-1310 (1990).

- A variant polypeptide can differ in amino acid sequence by one or more
- 20 substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities, for example, in histone deacetylase activity or transcription repression activity. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in
- 25 non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncations or a
- 30 substitution, insertion, inversion, or deletion in a critical residue or critical region, such critical regions include the HDAC domains, which provide the polypeptide

with deacetylase activity, as shown in the nucleic acid sequences of FIGS. 1A-1G, as well as in the schematic of FIG. 4.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, Science, 244: 1081-1085 (1989)). The latter procedure introduces a single alanine mutation at each of the residues in the molecule (one mutation per molecule). The resulting mutant molecules are then tested for biological activity *in vitro*. Sites that are critical for polypeptide activity can also be determined by structural analysis, such as crystallization, nuclear magnetic resonance, or photoaffinity labeling (See Smith *et al.*, J. Mol. Biol., 224: 899-904 (1992); and de Vos *et al.* Science, 255: 306-312 (1992)).

The invention also includes HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptide fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 or a portion thereof and the complements thereof or other variants. The present invention also encompasses fragments of the variants of the polypeptides described herein. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides that are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100, or more amino acids in length) can comprise a domain, segment, or motif, for example, an HDAC domain, that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for

expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These
5 comprise an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to
10 the N-terminus or C-terminus of the polypeptide. In one embodiment, the fusion polypeptide does not affect the function of the polypeptide per se. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for
15 example, β -galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased by using a heterologous signal sequence. Therefore, in another
20 embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A 0464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262).
25 In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. (See Bennett *et al.*, Journal of Molecular Recognition, 8: 52-58 (1995) and Johanson *et al.*, The Journal of Biological Chemistry, 270,16: 9459-9471 (1995)). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of
30 the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclass (IgG, IgM, IgA, IgE).

- A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive nucleic acid fragments that can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, "Current Protocols in Molecular Biology," John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference herein). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.
- 15 The substantially pure, isolated, or substantially pure and isolated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques.
- 20 For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell, and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.
- 25 In general, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides of the present invention can be used as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using art-recognized methods. The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also
- 30 be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a receptor or a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues

in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in a diseased state. The polypeptides can be used to isolate a corresponding binding agent, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. The polypeptides
5 of the present invention can also be used as therapeutic agents.

NUCLEIC ACID MOLECULES OF THE INVENTION

The present invention also features isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules.

10 By a "histone deacetylase nucleic acid molecule" is meant a nucleic acid molecule that encodes a histone deacetylase polypeptide. Such histone nucleic acids include, for example, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule described in detail herein; an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or
15 SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2,
20 SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3,
25 SEQ ID NO: 5, or SEQ ID NO: 7; and an isolated nucleic acid molecule that has at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.

An *HDAC9* nucleic acid molecule is a nucleic acid molecule that encodes an
30 *HDAC9* polypeptide. In one embodiment, the *HDAC9* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 1; a complement of an isolated nucleic acid comprising SEQ ID NO: 1;

an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 2; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 1, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 1.

An *HDAC9a* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9a polypeptide. An *HDAC9a* nucleic acid molecule preferably has at least 55%, sequence identity to SEQ ID NO: 3. In one embodiment, the *HDAC9a* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 3; a complement of an isolated nucleic acid comprising SEQ ID NO: 3; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 4; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 3; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 3 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9a* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 3.

An *HDAC9(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9(ΔNLS) polypeptide. In one embodiment, the *HDAC9(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 5; a complement of an isolated nucleic acid comprising SEQ ID NO: 5; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 6; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 6; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 6; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 5; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 5 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the

10 *HDAC9(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 5.

An *HDAC9a(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9a(ΔNLS)* polypeptide. In one embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the

15 nucleic acid sequence of SEQ ID NO: 7; a complement of an isolated nucleic acid comprising SEQ ID NO: 7; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that

20 encodes SEQ ID NO: 8; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 7; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 7 or a complement thereof, as determined using the BLAST

25 program and parameters described herein. In another embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 7.

An "*HDRP(ΔNLS)* nucleic acid molecule" is a nucleic acid molecule that encodes an *HDRP(ΔNLS)* polypeptide. In one embodiment, the *HDRP(ΔNLS)*

30 nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 10; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ
5 ID NO: 9 or a complement thereof, as determined using the BLAST program and parameters described herein.. In another embodiment, the *HDRP(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 9.

The isolated nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can
10 be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense, strand or the non-coding, or antisense, strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example). Additionally, the
15 nucleic acid molecule can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

20 An "isolated," "substantially pure," or "substantially pure and isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA or cDNA library). For example, an isolated nucleic acid of the invention may
25 be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system, or reagent mix. In other
30 circumstances, the material may be purified to essential homogeneity, for example, as determined by agarose gel electrophoresis or column chromatography such as

HPLC. Preferably, an isolated nucleic acid molecule comprises at least about 50, 80, or 90% (on a molar basis) of all macromolecular species present.

With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb, or 0.1 kb of nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector are included in the definition of "isolated" as used herein.

Isolated nucleotide molecules also include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the gene in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to variant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that are not necessarily found in nature but that encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Thus, for

example, DNA molecules that comprise a sequence that is different from the naturally-occurring *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide sequence but which, due to the degeneracy of the genetic code, encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or

5 *HDRP(ΔNLS)* polypeptide of the present invention are also the subject of this invention.

The invention also encompasses *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of an

10 *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Such variants can be naturally-occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion, and substitution of one or more

15 nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,

20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers.

Other alterations of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules of the invention can

25 include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, and carbamates), charged linkages (*e.g.*, phosphorothioates or phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine or psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids).

30 Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequences via hydrogen bonding and other chemical

interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that hybridize under
5 high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (e.g., nucleic acid molecules that specifically hybridize to a nucleotide sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein that hybridize under high stringency hybridization
10 conditions (e.g., for selective hybridization) to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and the complement of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the invention includes variants described herein that hybridize under high stringency
15 hybridization conditions (e.g., for selective hybridization) to a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 (*HDAC9*), SEQ ID NO: 4 (*HDAC9a*), SEQ ID NO: 6 (*HDAC9(ΔNLS)*), SEQ ID NO: 8 (*HDAC9a(ΔNLS)*), or SEQ ID NO: 10 (*HDRP(ΔNLS)*). In a preferred embodiment, the variant that hybridizes under high stringency hybridizations encodes a polypeptide that has a
20 biological activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide (e.g., histone deacetylase activity or transcription repression activity).

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (e.g., under high stringency conditions). "Specific hybridization," as
25 used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (e.g., when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for
30 hybridization is a term of art that refers to the incubation and wash conditions, e.g., conditions of temperature and buffer concentration, that permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be

perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used that distinguish perfectly complementary nucleic acids from those of less

5 complementarity. "High stringency conditions," "moderate stringency conditions," and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (See Ausubel *et al.*, *supra*, the entire teachings of which are incorporated by reference herein). The exact conditions that determine the stringency of

10 hybridization depend not only on ionic strength (*e.g.*, 0.2XSSC or 0.1XSSC), temperature (*e.g.*, room temperature, 42°C or 68°C), and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences, and the frequency of occurrence of

15 subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or

20 more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions that will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

25 Exemplary conditions are described in Krause and Aaronson, *Methods in Enzymology*, 200:546-556 (1991). Also, in, Ausubel, *et al.*, *supra*, which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the

30 lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the

sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of 17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate, or low stringency, depending on the level of mismatch sought.

5 For example, a low stringency wash can comprise washing in a solution containing 0.2XSSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2XSSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1XSSC/0.1%SDS
10 for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

15 To determine the percent homology or identity of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of one polypeptide or nucleic acid molecule for optimal alignment with the other polypeptide or nucleic acid molecule). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide
20 positions are then compared, as described above.

The present invention also provides isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1,
25 SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 4, SEQ
30 ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10. The nucleic acid fragments of the invention are at least about 15, preferably, at least about 18, 20, 23, or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer

fragments, for example, 30 or more nucleotides in length, that encode antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described above.

In a related aspect, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*,
5 and *HDRP(ΔNLS)* nucleic acid fragments of the invention are used as probes or
primers in assays such as those described herein. "Probes" or "primers" are
oligonucleotides that hybridize in a base-specific manner to a complementary strand
of nucleic acid molecules. Such probes and primers include polypeptide nucleic
acids, as described in Nielsen *et al.*, Science, 254, 1497-1500 (1991). As also used
10 herein, the term "primer" in particular refers to a single-stranded oligonucleotide that
acts as a point of initiation of template-directed DNA synthesis using well-known
methods (*e.g.*, PCR, LCR) including, but not limited to those described herein.

Typically, a probe or primer comprises a region of nucleotide sequence that
hybridizes to at least about 15, typically about 20-25, and more typically about 40,
15 50 or 75, consecutive nucleotides of a nucleic acid molecule comprising a
contiguous nucleotide sequence selected from: SEQ ID NO: 1, SEQ ID NO: 3, SEQ
ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, the complement of any of SEQ ID NO: 1,
SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and a sequence
encoding an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6,
20 SEQ ID NO: 8, or SEQ ID NO: 10.

In preferred embodiments, a probe or primer comprises 100 or fewer
nucleotides, preferably, from 6 to 50 nucleotides, and more preferably, from 12 to 30
nucleotides. In other embodiments, the probe or primer is at least 70% identical to
the contiguous nucleotide sequence or to the complement of the contiguous
25 nucleotide sequence, preferably, at least 80% identical, more preferably, at least 90%
identical, even more preferably, at least 95% identical, or even capable of selectively
hybridizing to the contiguous nucleotide sequence or to the complement of the
contiguous nucleotide sequence. Often, the probe or primer further comprises a
label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

30 The nucleic acid molecules of the invention such as those described above
can be identified and isolated using standard molecular biology techniques and the
sequence information provided in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5,

SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and/or SEQ ID NO: 10. For example, nucleic acid molecules can be amplified and isolated by the polymerase chain reaction using synthetic oligonucleotide primers designed based on one or more of the nucleic acid sequences provided above and/or the complement of those sequences. Or such nucleic acid molecules may be designed based on nucleotide sequences encoding one or more of the amino acid sequences provided in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H.A. Erlich, Freeman Press, NY, NY, (1992); PCR Protocols: A Guide to Methods and Applications (Eds. Innis *et al.*, Academic Press, San Diego, CA, (1990); Mattila *et al.*, Nucleic Acids Res., 19: 4967 (1991); Eckert *et al.*, PCR Methods and Applications, 1: 17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford)); and U.S. Patent No. 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA, or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (See Wu and Wallace, Genomics, 4:560 (1989), Landegren *et al.*, Science, 241:1077 (1988)), transcription amplification (Kwoh *et al.*, Proc. Natl. Acad. Sci. USA, 86:1173 (1989)), and self-sustained sequence replication (See Guatelli *et al.*, Proc. Nat. Acad. Sci. USA, 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, that produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be radiolabeled and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX, or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleotide sequence of nucleic acid molecules of the present

invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, Molecular Cloning, A Laboratory Manual (2nd Ed., CSHP, New York (1989)); Zyskind *et al.*, Recombinant DNA Laboratory Manual, (Acad. Press, (1988)). Using these or similar methods, the
5 polypeptide and the DNA encoding the polypeptide can be isolated, sequenced, and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or a portion of those
10 sequences, and/or the complement of those portion or sequences, and/or a sequence encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or encoding a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Such antisense nucleic acid molecules can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability
15 of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).
25

In general, the isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid sequences of the invention can be used as molecular weight markers on Southern blots, and as chromosome markers that are labeled to map related gene positions. The nucleic acid sequences can also be used to compare
30 with endogenous DNA sequences in patients to identify genetic disorders (*e.g.*, a predisposition for or susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease), and as probes, such as to hybridize and

discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid molecules of the present invention can also be used as therapeutic agents.

By a "cell proliferation disease" is meant a disease that is caused by or results in undesirably high levels of cell division, undesirably low levels of apoptosis, or both. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell proliferation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell proliferation diseases.

By a "cell differentiation disease" is meant a disease that is caused by or results in undesirably low levels of cell differentiation, or by undesirably high levels of cell differentiation. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell differentiation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell differentiation diseases.

By an "apoptotic disease" is meant a condition in which the apoptotic response is abnormal. This may pertain to a cell or a population of cells that does not undergo cell death under appropriate conditions. For example, normally a cell will die upon exposure to apoptotic-triggering agents, such as chemotherapeutic agents, or ionizing radiation. When, however, a subject has an apoptotic disease, for example, cancer, the cell or a population of cells may not undergo cell death in response to contact with apoptotic-triggering agents. In addition, a subject may have an apoptotic disease when the occurrence of cell death is too low, for example, when the number of proliferating cells exceeds the number of cells undergoing cell death, as occurs in cancer when such cells do not properly differentiate.

An apoptotic disease may also be a condition characterized by the occurrence of undesirably high levels of apoptosis. For example, certain neurodegenerative diseases, including but not limited to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, restenosis, stroke, and ischemic

brain injury are apoptotic diseases in which neuronal cells undergo undesired cell death.

Other diseases for which the polypeptides and nucleic acid molecules of the present invention may be useful for diagnosing and/or treating include, but are not
5 limited to Huntington's disease.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules of the present invention can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or
10 elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute
15 biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

In addition, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization, or therapeutic use,
20 or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (e.g., reagent kits) for use in the screening and/or diagnostic assays described herein.

25 Standard techniques, such as the polymerase chain reaction (PCR) and DNA hybridization, may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs in other species, for example, mammalian homologs. *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs may be readily identified using low-stringency DNA
30 hybridization or low-stringency PCR with human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* probes or primers. Degenerate primers encoding human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or

HDRP(Δ NLS) polypeptides may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs by RT-PCR.

Alternatively, additional *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs can be identified by utilizing
5 consensus sequence information for *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* polypeptides to search for similar polypeptides in other species. For example, polypeptide databases for other species can be searched for proteins with the HDAC domains described herein. Candidate polypeptides containing such a motif can then be tested for their *HDAC9*, *HDAC9a*,
10 *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* biological activities, using methods described herein.

EXPRESSION OF THE NUCLEIC ACID MOLECULES OF THE INVENTION

Another aspect of the invention pertains to nucleic acid constructs containing
15 an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule, for example, one selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 (or portions thereof). Yet another aspect of the invention
20 pertains to *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, and *HDRP(Δ NLS)* nucleic acid constructs containing a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation.

25 As used herein, the term "vector" or "construct" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral
30 genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal

mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in

- 5 recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

- Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals).
- 20 Such regulatory sequences are described, for example, in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences).

- It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce
- 30 polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells, such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, 5 *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example, using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms 10 "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included 15 within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast, or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells, human 293T cells, HeLa cells, NIH 3T3 cells, and mouse 20 erythroleukemia (MEL) cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of 25 art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

30 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select

these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin, or methotrexate. Nucleic acid molecules encoding a selectable
5 marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

- 10 A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector
15 encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

- The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is
20 a fertilized oocyte or an embryonic stem cell into which an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule of the invention has been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which
25 endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleotide sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity.

- As used herein, a “transgenic animal” is a non-human animal, preferably, a
30 mammal, more preferably, a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians. A

- transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a “homologous recombina-
- 5 recombinant animal” is a non-human animal, preferably, a mammal, more preferably, a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.
- 10 Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191, and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986)). Methods for
- 15 constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in Bio/Technology*, 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*,
- 20 *Nature*, 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

ANTIBODIES OF THE INVENTION

- Polyclonal and/or monoclonal antibodies that selectively bind one form of an
- 25 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide but not another form of the polypeptide are also provided. Antibodies are also provided that bind a portion of either the variant or reference HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide that contains the polymorphic site or sites.
- 30 In another aspect, the invention provides antibodies to each of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptides and polypeptide fragments of the invention, *e.g.*, having an amino acid sequence encoded

by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or another variant, or portion thereof).

The term "purified antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that selectively binds an antigen. A molecule that selectively binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample that naturally contains the polypeptide. Preferably the antibody is at least 60%, by weight, free from proteins and naturally occurring organic molecules with which it naturally associated. More preferably, the antibody preparation is at least 75% or 90%, and most preferably, 99%, by weight, antibody. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments that can be generated by treating the antibody with an enzyme such as pepsin.

The invention provides polyclonal and monoclonal antibodies that selectively bind to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition," as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the

blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to
5 prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature*, 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today*, 4:72 (1983)), the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96 (1985)) or trioma techniques. The
10 technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.*, (eds.) John Wiley & Sons, Inc., New York, NY (1994)). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to
15 identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current Protocols in*
20 *Immunology, supra*; Galfre *et al.*, (1977) *Nature*, 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.*, 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

25 Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin
30 library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage

Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology*, 9:1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas*, 3:81-85 (1992); Huse *et al.*, *Science*, 246:1275-1281 (1989); and Griffiths *et al.*, *EMBO J.*, 12:725-734 (1993).

10 Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

15 In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide.

25 The antibodies of the present invention can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, and acetylcholinesterase; examples of suitable

prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; an example of a luminescent material includes luminol; examples of
5 bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , and ^3H .

DIAGNOSTIC AND SCREENING ASSAYS OF THE INVENTION

The present invention also pertains to diagnostic assays for assessing *HDAC*
10 *9 HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene expression, or for assessing activity of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides of the invention. In one embodiment, the assays are used in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a cell proliferation disease,
15 an apoptotic disease, or a cell differentiation disease, or is at risk for (has a predisposition for or a susceptibility to) developing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The invention also provides for prognostic (or predictive) assays for determining whether an individual is susceptible to developing a cell proliferation disease, an apoptotic disease, or a cell
20 differentiation disease. For example, mutations in the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of symptoms associated with a cell proliferation disease, an apoptotic disease, or a cell
25 differentiation disease.

Another aspect of the invention pertains to assays for monitoring the influence of agents, or candidate compounds (*e.g.*, drugs or other agents) on the nucleic acid molecule expression or biological activity of polypeptides of the invention, as well as to assays for identifying candidate compounds that bind to an
30 HDAC9, HDAC9a polypeptide, an HDAC9(ΔNLS) polypeptide, an HDAC9a(ΔNLS) polypeptide, or an HDRP(ΔNLS) polypeptide. These and other assays and agents are described in further detail in the following sections.

DIAGNOSTIC ASSAYS

HDAC9, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules, probes, primers, polypeptides, and antibodies to an *HDAC9*,
5 an *HDAC9a* protein, an *HDAC9(ΔNLS)* protein, an *HDAC9a(ΔNLS)* protein, or an *HDRP(ΔNLS)* protein can be used in methods of diagnosis of a susceptibility to, or likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as well as in kits useful for diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

10 In one embodiment of the invention, diagnosis of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The polymorphism can be a mutation in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, such as the
15 insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift mutation; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of
20 one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene; duplication of all or a part of the gene; transposition of all or a part of the gene; or rearrangement of all or a part of the gene, or a change in the expression pattern of the various *HDAC9* isoforms. More than one such mutation may be present in a single nucleic acid
25 molecule.

Such sequence changes cause a mutation in the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, if the mutation is a frame shift mutation, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a
30 premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can be a synonymous

mutation in one or more nucleotides (*i.e.*, a mutation that does not result in a change in the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). Such a polymorphism may alter sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid molecule. HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) that has any of the mutations described above is referred to herein as a "mutant nucleic acid molecule."

In a first method of diagnosing a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see Ausubel, *et al.*, *supra*). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a cell proliferation disease, an apoptotic disease, or a cell differentiation disease (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source that contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract, or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present, and/or to determine which variant(s) encoded by HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present. The presence of the polymorphism or variant(s) can be indicated by hybridization of the gene in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe," as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or contains a nucleic acid encoding a particular variant of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). The probe can be any of the nucleic acid

molecules described above (e.g., the entire nucleic acid molecule, a fragment, a vector comprising the gene, a probe, or primer, etc.).

To diagnose a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, a hybridization sample is formed by contacting the test sample containing *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, with at least one nucleic acid probe. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250, or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9; or can be a nucleic acid molecule encoding all or a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Other suitable probes for use in the diagnostic assays of the invention are described above (see, e.g., probes and primers discussed under the heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. "Specific hybridization," as used herein, indicates exact hybridization (e.g., with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the test sample, then *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* has the

polymorphism, or is the variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In Northern analysis (see Current Protocols in Molecular Biology, Ausubel, *et al.*, *supra*), the hybridization methods described above are used to identify the presence of a polymorphism or of a particular variant, associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

For representative examples of use of nucleic acid probes, see, for example, U.S. Patent Nos. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T, or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen *et al.*, *Bioconjugate Chemistry*, 5 (1994), American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a gene having a polymorphism associated with a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. Hybridization of the PNA probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is diagnostic for a decreased

susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another method of the invention, mutation analysis by restriction digestion can be used to detect a mutant nucleic acid molecule, or nucleic acid molecules
5 containing a polymorphism(s), if the mutation or polymorphism in the gene results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*
10 (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see Current Protocols in Molecular Biology, *supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the mutation or polymorphism in *HDAC9*,
HDAC9a, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and therefore indicates the presence or absence of this decreased susceptibility to a cell
15 proliferation disease, an apoptotic disease, or a cell differentiation disease.

Sequence analysis can also be used to detect specific polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid molecule, and/or its
20 flanking sequences, if desired. The sequence of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a fragment of the any of those nucleic acid molecules, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* cDNA, or a fragment of any of those cDNAs, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA,
25 or a fragment of any of those mRNAs, is determined, using standard methods. The sequence of the above gene, gene fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid molecule, cDNA (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a nucleic acid sequence encoding the protein of SEQ ID
30 NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* indicates that the

individual has a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Allele-specific oligonucleotides can also be used to detect the presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)*, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki *et al.*, Nature (London) 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, preferably
10 approximately 15-30 base pairs, that specifically hybridizes to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and that contains a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An allele-specific oligonucleotide probe that is specific for particular polymorphisms in *HDAC9*,
15 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be prepared, using standard methods (see Current Protocols in Molecular Biology, *supra*).

To identify polymorphisms in the gene that are associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease a test sample of DNA is obtained from the individual. PCR
20 can be used to amplify all or a fragment of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and its flanking sequences. The DNA containing the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a fragment of any of those genes) is dot-blotted, using standard methods (see Current Protocols in Molecular Biology, *supra*), and the blot is
25 contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is
30 therefore indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, in one embodiment, an

5 oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "GENECHIPS™," have been generally described in the art, for example, U.S. Patent No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and 92/10092.

10 These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, Science, 251:767-777 (1991), Pirrung *et al.*, U.S. Patent No. 5,143,854; PCT Publication No. WO 90/15070; Fodor *et al.*, PCT Publication No. WO 92/10092,

15 and U.S. Patent No. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Patent No. 5,384,261, the entire teachings of which are incorporated by reference herein.

Once an oligonucleotide array is prepared, a nucleic acid of interest is

20 hybridized to the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, Published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Patent No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified

25 polymorphic markers is amplified by well known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate

30 conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence

hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array.

Although primarily described in terms of a single detection block, *e.g.*, for detection of a single polymorphism, arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. In alternate arrangements, it will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional descriptions of the use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patent Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein.

Other methods of nucleic acid analysis can be used to detect polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Representative methods include direct manual sequencing (Church and Gilbert *Proc. Natl. Acad. Sci. USA* 81: 1991-1995, (1988); Sanger *et al.*, *Proc. Natl. Acad. Sci.* 74: 5463-5467 (1977); Beavis *et al.*, U.S. Patent No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 232-236 (1991)), mobility shift analysis (Orita *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, *Cell* 15: 25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78: 5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 4397-4401 (1985)); RNase protection assays (Myers *et al.*, *Science* 230: 1242 (1985)); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can also be made by examining the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid, for example, using in situ hybridization techniques known to one skilled in the art, or by examining the level of expression, activity, and/or composition of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunohistochemistry, and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid or in the expression and/or an alteration in composition of the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or for the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. An alteration in expression of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or variant thereof). In a preferred embodiment, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a particular pattern of variants. Preferably, increased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or increased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates an increased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell

differentiation disease. Alternatively, decreased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or decreased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample

5 known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates a decreased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Both quantitative and qualitative alterations can also be present. An

10 “alteration” or “modulation” in the polypeptide expression, activity, or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is

15 from the same type of cells), and is from an individual who is not affected by a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 Similarly, the presence of one or more different variants in the test sample, or the presence of significantly different amounts of different variants in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

It is understood that alterations or modulations in polypeptide expression or

25 function can occur in varying degrees. For example, an alteration or modulation in expression can be an increase, for example, by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the alteration or modulation in polypeptide expression can be a decrease, for example, by at least 10%, at least 40%, 50%, or 75%, or by at least 90%, relative to the control.

30 Various means of examining expression or composition of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and

immunoassays (*e.g.*, David *et al.*, U.S. Patent No. 4,376,110) such as immunoblotting (see also Ausubel *et al.*, *supra*; particularly chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be
5 used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled," with regard to the antibody, is intended to encompass direct labeling of the antibody by coupling (*i.e.*, physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reacting it with another
10 reagent that is directly labeled. An example of indirect labeling is detection of a primary antibody using a fluorescently labeled secondary antibody.

Western blotting analysis, using an antibody as described above that specifically binds to a mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically
15 binds to a non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically binds to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, can be used to identify the presence in a test sample of a particular variant of a polypeptide encoded by a polymorphic or mutant *HDAC9*, *HDAC9a*,
20 *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, or the absence in a test sample of a particular variant or of a polypeptide encoded by a non-polymorphic or non-mutant gene. The presence of a polypeptide encoded by a polymorphic or mutant gene, or the absence of a polypeptide encoded by a non-polymorphic or non-mutant gene, is diagnostic for a decreased susceptibility to a cell proliferation
25 disease, an apoptotic disease, or a cell differentiation disease, as is the presence (or absence) of particular variants encoded by the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule.

In one embodiment of this method, the level or amount of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test
30 sample is compared with the level or amount of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A level or amount of the polypeptide in the test sample that is higher or

lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, and is diagnostic for a decreased susceptibility to a cell proliferation
5 disease, an apoptotic disease, or a cell differentiation disease.

Alternatively, the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test sample is compared with the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A difference in the composition of
10 the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample (e.g., the presence of different variants), is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample
15 and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 Kits (e.g., reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including, for example, hybridization probes or primers as described herein (e.g., labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (e.g., for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to a mutant or to
25 non-mutant (native) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, means for amplification of nucleic acids comprising HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or means for analyzing the nucleic acid sequence of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or for analyzing the amino acid sequence of an
30 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, etc.

SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as “screening assays”) for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing the nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleotide sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleotide sequence is completely complementary to a part of the nucleic acid molecule of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*.

In any of the above embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically binds to the

polypeptide of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (*e.g.*, an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide.

- 5 In another embodiment, the invention provides methods for identifying agents or compounds (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter or modulate (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or that otherwise interact with the polypeptides
- 10 herein. For example, such compounds can be compounds or agents that bind to polypeptides described herein (*e.g.*, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrates or agents); that have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or that change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to
- 15 interact with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) binding agents; or that alter post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell
- 20 surface; or agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.). In one example, the binding agent is a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease binding agent. As used herein, by a "cell proliferation disease binding agent," an "apoptotic disease binding agent," or a "cell differentiation disease
- 25 binding agent" is meant an agent as described herein that binds to a polypeptide of the present invention and modulates a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The modulation can be an increase or a decrease in the severity or progression of the disease. In addition, a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease
- 30 binding agent includes an agent that binds to a polypeptide that is upstream (earlier) or downstream (later) of the cell signaling events mediated by a polypeptide of the

present invention, and thereby modulates the overall activity of the signaling pathway; in turn, the disease state is modulated.

The candidate compound can cause an increase in the activity of the polypeptide. For example, the activity of the polypeptide can be increased by at least
5 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the polypeptide activity can be a decrease, for example, by at least 10%, at least 20%, 40%, 50%, or 75%, or by at least 90%, relative to the control.

In one embodiment, the invention provides assays for screening candidate compounds or test agents to identify compounds that bind to or modulate the activity
10 of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. As used herein, a "candidate compound" or "test agent" is a chemical molecule, be it naturally-occurring or artificially-derived, and includes, for example, peptides, proteins, synthesized molecules, for example, synthetic organic molecules, naturally-occurring molecule, for example, naturally
15 occurring organic molecules, nucleic acid molecules, and components thereof.

In general, candidate compounds for uses in the present invention may be identified from large libraries of natural products or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise
20 source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as
25 modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available, e.g., from Brandon Associates (Merrimack, NH) and
30 Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova

(Slough, UK), Harbor Branch Oceanographics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are generated, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. For example, candidate
5 compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological
10 library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des., 12: 145 (1997)). Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

15 In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their activities should be employed whenever possible.

20 When a crude extract is found to modulate (i.e., stimulate or inhibit) the expression and/or activity of the nucleic acids and or polypeptides of the present invention, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and
25 identification of a chemical entity within the crude extract having an activity that stimulates or inhibits nucleic acid expression, polypeptide expression, or polypeptide biological activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous
30 extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value may be subsequently analyzed

using animal models for diseases in which it is desirable to alter the activity or expression of the nucleic acids or polypeptides of the present invention.

In one embodiment, to identify candidate compounds that alter the biological activity, for example, the enzymatic activity or transcriptional repression activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, a cell, tissue, cell lysate, tissue lysate, or solution containing or expressing an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or another variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*), or a fragment or derivative thereof (as described above), can be contacted with a candidate compound to be tested under conditions suitable for enzymatic reaction or transcriptional repression reaction, as described herein.

Alternatively, the polypeptide can be contacted directly with the candidate compound to be tested. The level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is assessed (*e.g.*, the level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is measured, either directly or indirectly), and is compared with the level of biological activity in a control (*i.e.*, the level of activity of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or active fragment or derivative thereof in the absence of the candidate compound to be tested, or in the presence of the candidate compound vehicle only). If the level of the biological activity in the presence of the candidate compound differs, by an amount that is statistically significant, from the level of the biological activity in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. For example, an increase in the level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) enzymatic or transcriptional repression activity relative to a control, indicates that the candidate compound is a compound that enhances (is an agonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity. Similarly,

- a decrease in the enzymatic level or transcriptional repression level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity relative to a control, indicates that the candidate compound is a compound that inhibits (is an antagonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or
- 5 HDRP(Δ NLS) activity. In another embodiment, the level of biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or derivative or fragment thereof in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level of the biological activity in the presence of the candidate
- 10 compound that differs from the control level by an amount that is statistically significant indicates that the compound alters HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity.

- The present invention also relates to an assay for identifying compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or
- 15 *HDRP(Δ NLS)* nucleic acid molecule (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid molecule or that otherwise interact with the nucleic acids described herein, as well as compounds
- 20 identifiable by the assays. For example, a solution containing a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide can be contacted with a candidate compound to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution
- 25 that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different variants) is assessed, and is compared with the
- 30 level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* expression in the absence of the candidate compound, or in the presence of the candidate

- compound vehicle only). If the level and/or pattern in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a
- 5 compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Enhancement of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of *HDAC9*,
- 10 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an antagonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level and/or pattern of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide(s) (e.g., different variants) in the presence of the
- 15 candidate compound to be tested, is compared with a control level and/or pattern that has previously been established. A level and/or pattern in the presence of the candidate compound that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*
- 20 expression.

- In another embodiment of the invention, compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or that otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic
- 25 acid encoding the promoter region of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene operably linked to a reporter gene. After contact with a candidate compound to be tested, the level of expression of the reporter gene (e.g., the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (i.e., the level of the expression
- 30 of the reporter gene in the absence of the candidate compound, or in the presence of the candidate compound vehicle only). If the level in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from

the level in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as indicated by its ability to alter expression of a gene that is operably linked to the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene promoter. Enhancement of the expression of the reporter indicates that the compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of the expression of the reporter indicates that the compound is an antagonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level of expression of the reporter in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level in the presence of the candidate compound that differs from the control level by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression.

Compounds that alter the amounts of different variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (e.g., a compound that enhances activity of a first variant, and that inhibits activity of a second variant), as well as compounds that are agonists of activity of a first variant and antagonists of activity of a second variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a candidate compound on the activity of a polypeptide in relation to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate, for example, an inhibitor of histone deacetylase activity. These inhibitors fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids (e.g., SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such assays and compounds can be found in U.S. Patent Nos. 5,369,108, issued on

November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, *supra*; Saito *et al.*, *supra*; Furamai *et al.*, *supra*; Komatsu *et al.*, *supra*; Su *et al.*, *supra*; Lee *et al.*, *supra* and Suzuki *et al.* *supra*, the entire content of all of which are hereby incorporated by reference.

In one example, a cell or tissue that expresses or contains a compound that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (herein referred to as an "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate," which can be a polypeptide or other molecule that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)) is contacted with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) in the presence of a candidate compound, and the ability of the candidate compound to alter the interaction between HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) and the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP (Δ NLS) substrate is determined, for example, by assaying activity of the polypeptide. Alternatively, a cell lysate or a solution containing the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, can be used. A compound that binds to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can alter the interaction by interfering with, or enhancing the ability of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) to bind to, associate with, or otherwise interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate.

Determining the ability of the candidate compound to bind to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can be accomplished, for example, by coupling the candidate compound with a radioisotope or enzymatic label such that binding of the candidate compound to the polypeptide can be determined by detecting the labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of

radioemmission or by scintillation counting. Alternatively, candidate compound can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

5 It is also within the scope of this invention to determine the ability of a candidate compound to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a candidate compound with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS),
10 HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate without the labeling of either the candidate compound, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate (McConnell *et al.*, (1992) Science, 257: 1906-1912). As used herein, a "microphysiometer" (*e.g.*, CYTOSENSOR™) is an analytical
15 instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

 In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS),
20 HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields and Song, Nature 340: 245-246 (1989)) can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides. In such a yeast two-hybrid system, vectors are
25 constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as
30 lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used that includes a nucleic acid encoding a DNA binding domain and an HDAC9, HDAC9a,

HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof, and a second vector is used that includes a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a polypeptide that potentially may interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof (e.g., an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide substrate or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (e.g., mating conditions such as used in the MATCHMAKER™ system from Clontech) allows identification of colonies that express the markers of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). These colonies can be examined to identify the polypeptide(s) that interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or fragment or derivative thereof. Such polypeptides may be useful as compounds that alter the activity or expression of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a candidate compound to the polypeptide, or interaction of the polypeptide with a substrate in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (e.g., a glutathione-S-transferase fusion protein) can be provided that adds a domain that allows HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, tissue, tissue lysate, or solution containing a nucleic acid encoding HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is contacted with a candidate compound and the expression of appropriate mRNA or polypeptide (*e.g.*, variant(s)) in the cell, cell lysate, tissue, or tissue lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the candidate compound is compared to the level of expression of mRNA or polypeptide(s) in the absence of the candidate compound, or in the presence of the candidate compound vehicle only. The candidate compound can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

This invention further pertains to novel compounds identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use a compound identified as described herein in an appropriate animal model. For example, a compound identified as described herein (*e.g.*, a candidate compound that is a modulating compound such as an antisense nucleic acid molecule, a specific antibody, or a polypeptide substrate) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a compound. Alternatively, a compound identified as described herein can be used in an animal model to determine the mechanism of action of such a compound. Furthermore, this invention pertains to uses of novel compounds identified by the above-described screening assays for treatments as described herein. In addition, a compound identified as described herein can be used to alter activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or to

alter expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, by contacting the polypeptide or the nucleic acid molecule (or contacting a cell comprising the polypeptide or the nucleic acid molecule) with the compound identified as described herein.

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PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleotides encoding the polypeptides described herein; comprising polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*); and/or comprising a compound that alters (*e.g.*, increases or decreases) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression or *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity as described herein. For instance, a polypeptide, protein, fragment, fusion protein or prodrug thereof, or a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate or binding partner, can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

25 Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic

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pressure, buffers, coloring, flavoring and/or aromatic substances and the like that do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid
5 solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate,
10 etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable
15 devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other compounds.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human
20 beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free
25 concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active compound. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be
30 provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a

dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., that are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The compound may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Compounds described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The compounds are administered in a therapeutically effective amount. The amount of compounds that will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, that notice

reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the
5 patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the compounds can be separated, mixed together in any combination, present in a single vial or tablet. Compounds assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a
10 dosage that is dependent on the individual pharmacodynamics of each compound and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

The present invention also pertains to methods of treatment (prophylactic,
15 diagnostic, and/or therapeutic) for a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, using an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound. An "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound" is a compound that alters (*e.g.*, enhances or inhibits) HDAC9, HDAC9a,
20 HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity and/or *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule expression, as described herein (*e.g.*, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) agonist or antagonist).
HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)
25 therapeutic compounds can alter HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity or nucleic acid molecule expression by a variety of means, such as, for example, by providing additional HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or by upregulating the transcription or translation of the *HDAC9*,
30 *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule; by altering post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide; by altering

transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants; or by interfering with *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity (*e.g.*, by binding to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide), or by downregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule. Representative *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds include the following: nucleic acids or fragments or derivatives thereof described herein, particularly nucleotides encoding the polypeptides described herein and vectors comprising such nucleic acids (*e.g.*, a nucleic acid molecule, cDNA, and/or RNA, such as a nucleic acid encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or active fragment or derivative thereof, or an oligonucleotide; for example, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or fragments or derivatives thereof); polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10 and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or fragments or derivatives thereof); *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrates; peptidomimetics; fusion proteins or prodrugs thereof; antibodies (*e.g.*, an antibody to a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as described above); ribozymes; other small molecules; and other compounds that alter (*e.g.*, enhance or inhibit) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression or polypeptide activity, for example, those compounds identified in the screening methods described herein, or that regulate transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants (*e.g.*,

compounds that affect which variants are expressed, or that affect the amount of each variant that is expressed. More than one HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be used concurrently, if desired.

- 5 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound that is a nucleic acid is used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease,
- 10 and also lessening the severity or frequency of symptoms of the disease. The therapy is designed to alter (*e.g.*, inhibit or enhance), replace or supplement activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in an individual. For example, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be administered in
- 15 order to upregulate or increase the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or, conversely, to downregulate or decrease the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or
- 20 *HDRP(Δ NLS)* nucleic acid molecule or specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). Upregulation or increasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could interfere with or compensate for the expression or activity of a defective gene
- 25 or another variant; downregulation or decreasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could minimize the expression or activity of a defective gene or the particular variant and thereby minimize the impact of the defective gene or the particular variant.
- 30 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease, such as by

ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount that will be therapeutically effective in the treatment of a particular individual's disorder or condition will depend on the symptoms and
5 severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each
10 patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In one embodiment, a nucleic acid of the invention (*e.g.*, a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, such as SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5,
15 SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or a variant, derivative or fragment thereof, such as a nucleic acid encoding the protein of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10) can
20 be used, either alone or in a pharmaceutical composition as described above. For example, *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) or a cDNA encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, either by itself or included within a vector, can be introduced into cells (either *in vitro* or *in vivo*) such that the cells produce native
25 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. If desired, cells that have been transformed with the gene or cDNA or a vector comprising the gene or cDNA can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells that, in nature, lack native *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) expression and
30 activity, or have mutant *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) expression and activity, or have expression of a disease-associated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) variant,

can be engineered to express an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or an active fragment of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (or a different variant of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). In a preferred embodiment, nucleic acid encoding the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an active fragment or derivative thereof, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells in an animal. Other gene transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral gene transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (e.g., microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used to introduce the desired nucleic acid molecule into a cell.

Alternatively, in another embodiment of the invention, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (e.g., an oligonucleotide as described below), can be used in "antisense" therapy, in which a nucleic acid (e.g., an oligonucleotide) that specifically hybridizes to the RNA and/or genomic DNA of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the RNA and/or DNA inhibits expression of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) nucleic acid molecule, e.g., by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. Alternatively, the antisense construct can be an oligonucleotide probe which is generated *ex vivo* and introduced

into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.* exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.*, *Biotechniques* 6: 958-976 (1988); and Stein *et al.*, *Cancer Res* 48: 2659-2668 (1988). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.* between the -10 and +10 regions of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequence, are preferred.

15 To perform antisense therapy, oligonucleotides (RNA, cDNA or DNA) are designed that are complementary to mRNA encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. The antisense oligonucleotides bind to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA transcripts and prevent translation. Absolute

20 complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to

25 hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

30 The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar

moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or compounds facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, Proc. Natl. Acad. Sci. USA 86: 6553-6556 (1989); Lemaitre *et al.*, Proc. Natl. Acad. Sci. USA 84: 648-652 (1987); PCT International Publication No. W088/09810)) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. W089/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, BioTechniques 6: 958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm. Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* transcripts and thereby prevent translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC, or viral vector can be used to prepare the recombinant DNA

construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systematically).

- Endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
- 5 *HDRP(ΔNLS)* expression can also be reduced by inactivating or “knocking out” *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequences or their promoters using targeted homologous recombination (*e.g.*, see Smithies *et al.*, Nature 317: 230-234 (1985); Thomas and Capecchi, Cell 51: 503-512 (1987); Thompson *et al.*, Cell 5: 313-321 (1989)). For example, a mutant,
- 10 non-functional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (either the coding regions or regulatory regions of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) can be
- 15 used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The recombinant DNA constructs can be
- 20 directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be increased using a similar method: Targeted homologous recombination can be used to insert a DNA construct comprising a non-mutant, functional *HDAC9*, *HDAC9a*,
- 25 *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*e.g.*, a gene having SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism), or a portion thereof, in place of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the cell, as described above. In another embodiment, targeted homologous
- 30 recombination can be used to insert a DNA construct comprising a nucleic acid that encodes an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide variant that differs from that present in the cell.

Alternatively, endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (i.e., the *HDAC9*,
5 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* promoter and/or enhancers) to form triple helical structures that prevent transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in target cells in the body. (See generally, Helene Anticancer Drug Des., 6(6): 569-84 (1991); Helene *et al.*, Ann. N.Y. Acad. Sci., 660: 27-36 (1992); and Maher, Bioassays 14(12): 807-15
10 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* proteins, can be used in the manipulation of tissue, e.g., tissue differentiation, both *in vivo* and for *ex vivo* tissue cultures. Furthermore, the antisense techniques (e.g., microinjection of antisense molecules,
15 or transfection with plasmids whose transcripts are anti-sense with regard to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or gene sequence) can be used to investigate role of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in developmental events, as well as the normal cellular function of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in adult tissue. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

In yet another embodiment of the invention, other *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds as described herein can also be used in the treatment or prevention of a cell
25 proliferation disease, an apoptotic disease, or a cell differentiation disease. The therapeutic compounds can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic compounds can be produced by a variety of means, including chemical synthesis; recombinant production; *in vivo* production
30 (e.g., a transgenic animal, such as U.S. Patent No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein.

A combination of any of the above methods of treatment (e.g., administration of non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in conjunction with antisense therapy targeting mutant *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or
5 *HDRP*(Δ NLS) mRNA; administration of a first variant encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) in conjunction with antisense therapy targeting a second encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS), can also be used.

In another embodiment, the invention is directed to *HDAC9*, *HDAC9a*,
10 *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) polypeptides for use as a medicament in therapy. For example, the nucleic acid molecules or polypeptides of the present invention can be used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In
15 addition, the *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) polypeptides described herein can be used in the manufacture of a medicament for the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 The invention will be further described by the following non-limiting examples. The teachings of all publications cited herein are incorporated herein by reference in their entirety.

EXEMPLIFICATION

25 *Cloning of cDNA encodes a novel HDAC, designated HDAC9*

HDAC9 was cloned by PCR and 3' rapid amplification of cDNA ends using primers designed from the sequence of human chromosome 7 whose translated product exhibited 80% identity to the HDAC domain of HDAC4, described in detail as follows.

30 Database analyses indicate that *HDRP* is located on chromosome 7 (7p15-p21). The human genome database (February 2001 release) of GenBank was searched using the human HDAC4 amino acid sequence. The TBLASTN program

was used to identify open reading frames downstream of *HDRP* on chromosome 7 that exhibit significant homology to the HDAC domain of HDAC4. Several fragments whose translated products exhibit over 58% identity were retrieved. Two sense primers (OL486, 5'-CCATGGAAACGGTACCCAGCAGGC-3' (SEQ ID NO: 16) and OL487, 5'-CACTCCATCGCTATGATGAAGGG-3' (SEQ ID NO: 17)) and antisense primers (OL484, 5'-AGTTCCTTCATCATAGCGATGG-3' (SEQ ID NO: 18) and OL485, 5'-AATGTACAGGATGCTGGGGT-3' (SEQ ID NO: 19)) each were designed based upon one of these fragments whose translated products matched amino acids 842-873 of HDAC4. RT-PCR was performed using each of the antisense primers and a sense primer (5'-CCCTTGCTAGCTGGTGGAGTTCCCTT-3' (SEQ ID NO: 20)) from the coding region of *HDRP* and human brain cDNA as a template. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 120 seconds.

3'-rapid amplification of cDNA ends was performed using the sense primer OL486 and adaptor primer 1 (Clontech), and marathon-ready cDNA from human brain (Clontech, Palo Alto, CA) according to the manufacturer's instruction. The products were re-amplified using nested sense primer OL487 and adaptor primer 2 (Clontech, Palo Alto, CA). PCR products were cloned into pGEM-T-easy vector (Promega, Madison, WI) and sequenced using an automated DNA sequencer at the DNA Sequencing Core Facility of the Memorial Sloan-Kettering Cancer Center, using DNA sequencing methods known to one of skill in the art.

Two cDNAs were cloned from the above-described methods. One cDNA (SEQ ID NO:1) encodes an HDAC9 protein that is 1011 amino acids in length. The other cDNA (SEQ ID NO: 3) encodes an HDAC9a protein that is 879 amino acids long. The cDNA sequence and amino sequence of *HDAC9* and *HDAC9a* are shown in FIGS. 1A-1G and FIGS. 2A-2B, respectively. Database analyses of these cDNAs against human genomic DNA sequences indicated that these two cDNAs are generated by alternatively splicing. An alignment of HDAC9, HDAC9a, HDRP, and HDAC4 is shown in FIGS. 3A-3C.

Each of the HDAC9 and HDAC9a nucleic acid sequences were cloned into the pFLAG-CMV-5b vector (Sigma) in frame with the C-terminal FLAG tag. Only

the coding regions plus three extra base pairs (ACC) of cDNA of the HDAC9 and HDAC9a nucleic acid sequences were included in the constructs. These constructs are referred to herein as HDAC9-FLAG and HDAC9a-FLAG, respectively. These constructs are contained in *E. coli*, and can readily be expressed. For HDAC9, the
5 insert is 3033 bp and for HDAC9a, the insert size is 2637 bp. Both HDAC9 and HDAC9a can be released with EcoRV and BamHI (whose sites have been incorporated in the primers to obtain HDAC9 and HDAC9a coding cDNA for cloning purpose) restriction enzyme digestion.

The *HDAC9* cDNA sequences from the known 5'-end of *HDRP* cDNA to the
10 3'-untranslated region cloned in this study cover over 511 kb of genomic DNA on chromosome 7. As shown in FIG. 4, the coding region cDNA of *HDAC9* resides in 23 exons spanning 458 kb of genomic sequence. Exons 21, 22, and 23 are one single exon in HDAC9a, but the middle exon that is numbered exon 22 in FIG. 4, containing an in-frame stop codon, is spliced out in HDAC9. In addition, exons 12
15 and 13 are a single exon used by HDRP. Exon 13 is spliced as part of an intron in HDAC9 and HDAC9a.

Further analysis revealed that exon 7, which contains a nuclear localization signal (NLS) is alternatively spliced in an HDRP isoform, creating HDRP(Δ NLS). RT-PCR analyses using primers based on sequences from exon 6 and exon 14
20 indicate that this alternative splicing event also occurs in *HDAC9* and/or *HDAC9a*. Thus, it is possible that at least 6 proteins can be generated from a single *HDAC9* gene by alternatively splicing of its RNA. The cDNA sequences and amino acid sequences for HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) are shown in FIGS. 1A-1O and 2A-2E, respectively.

25

HDAC9 mRNA is differentially expressed among human tissues

The expression of *HDAC9* mRNA was determined by Northern blot analysis using a human multiple tissue Northern blot (Clontech, Palo Alto, CA). Hybridization was performed according to the manufacturer's instruction using
30 ExPressHyb solution (Clontech, Palo Alto, CA). The 32 P-random priming labeled 3'-untranslated region common to both *HDAC9* and *HDAC9a* that shares no significant sequence homology with *HDRP* was used as a probe. Two transcripts at

9.8 and 4.1 kb were detected in all tissues examined (FIG. 6A). The 4.1 kb transcript is shorter than the 4.4 kb *HDRP* transcript (See Zhou, *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). A third transcript at 1.2 kb was detected in placenta (FIG. 6A). Similar to *HDRP* (See Zhou, X., *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)), high levels of *HDAC9* transcripts were detected in brain and skeletal muscle (FIG. 6A).

The distribution of alternatively spliced mRNA variants among tissues was examined by RT-PCR using primers (OL516 5'-TGTGTCATCGAGCTGGCTTC-3' (SEQ ID NO: 21) and OL517 5'-ATCTTCTGCAAGTGGCTCCA-3' (SEQ ID NO: 22)) spanning the alternatively spliced exon 22 and cDNA panel from the same tissues as the multiple tissue Northern blot. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 60 seconds. The expected sizes of PCR products were 680 base pairs for *HDAC9* and 993 base pairs for *HDAC9a*. The ratio of *HDAC9* and *HDAC9a* transcripts differed among tissues (FIG. 6B). In the placenta and kidney, the levels of the two transcripts were about the same (FIG. 6B). In the brain, heart, and pancreas, there were more transcripts of *HDAC9* than *HDAC9a*. In the other tissues examined, there were more *HDAC9a* transcripts than *HDAC9* transcripts (FIG. 6B). Under the conditions tested, *HDAC9* transcripts were undetectable in liver (FIG. 6B). The lung had an *HDAC9* product that was larger than expected and abundant. The lung also had low levels of *HDAC9* transcripts and *HDAC9a* transcripts (FIG. 6B). An additional PCR product was also amplified from cDNA of the pancreas; this product was than the expected products from *HDAC9* and *HDAC9a* (FIG. 6B). The identity of the different sized transcripts is unknown.

HDAC9 and HDAC9a possess histone deacetylase activity

HDAC9 was named based on sequence homology to *HDAC4* (FIGS. 3A-3C). To determine whether *HDAC9* and *HDAC9a* possess HDAC activity, an HDAC enzymatic assay was performed using anti-FLAG immunoprecipitated *HDAC9*-FLAG and *HDAC9a*-FLAG.

C-terminal FLAG-tagged *HDAC9* (*HDAC9*-FLAG) and *HDAC9a* (*HDAC9a*-FLAG) expression vectors were constructed using the pFLAG-CMV-5b

vector (Sigma) and PCR amplified coding regions of HDAC9 and HDAC9a in frame with the FLAG-tag to form pFLAG-CMV-5b-HDAC9 (plasmid VR1) and pFLAG-CMV-5b-HDAC9a (plasmid VR2). All constructs were confirmed by DNA sequencing.

- 5 Transfection of human kidney 293T cells, immunoprecipitation using anti-FLAG M2 Agarose (Sigma), Western blot analyses and dual luciferase assays were performed essentially as previously described by Zhou *et al.* (Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). Briefly, the cells (American Type Culture Collection) were cultured in DME HG medium (GIBCO/BRL) supplemented with 10%
10 (vol/vol) FBS at 37 °C in a 5% CO₂ atmosphere. Transient transfection was performed by using Lipofectamine (GIBCO/BRL) or Fugene 6 (Roche Molecular Biochemicals) according to the manufacturers' instructions. Cells were harvested 24 to 48 hours after transfection and lysed in IP lysis buffer (50 mM Tris-HCl, pH 7.5/120 mM NaCl/5 mM EDTA/0.5% NP-40) at 5 x 10⁷ cells per ml.
15 Immunoprecipitation with anti-FLAG M2-agarose (Sigma, St. Louis, MO) was performed according to the manufacturer's instructions. Immunoprecipitated proteins were released from the agarose beads by using FLAG-peptide and either used directly for HDAC enzymatic activity assays or resolved on SDS/PAGE for Western blot analyses. Anti-FLAG antibody was purchased from Sigma (St. Louis,
20 MO). Western blot analyses were performed using standard methods.

- HDAC9 and HDAC9a enzymatic activity were assessed with the HDAC Fluorescent Activity Assay/Drug Discovery Kit-AK-500 (BIOMOL Research Laboratories) using a FLUOR DE LYSTM that contains an acetylated lysine side chain as a substrate and immunoprecipitated HDAC9-FLAG and HDAC9a-FLAG
25 polypeptides according to the manufacturer's instruction and a SPECTRAMax[®] GEMINI XS microplate spectrofluorometer using the SOFTmax[®] PRO system (Molecular Devices) at excitation 355 nm and emission 460 nm with a cut off filter of 455 nm. Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with the substrate overnight at room temperature in a 96-well plate. The reaction was
30 stopped by addition of Fluor De LysTM Developer and samples were read with the fluorometer.

As shown in FIG. 7, both HDAC9-FLAG and HDAC9a-FLAG deacetylated the acetylated lysine of FLUOR DE LYSTM and the activity of HDAC9 and HDAC9a was comparable. To examine the activity of HDAC9 and HDAC9a, inhibition studies using TSA were carried out by preincubating HDAC9-FLAG and HDAC9a-FLAG with TSA for 15 minutes at room temperature. The assay was then carried out as stated above. As shown in FIG. 7, TSA inhibited HDAC9 and HDAC9a deacetylase activity. The inset gel in FIG. 7 shows the amount of protein used in the assay. SAHA, a potent HDAC inhibitor (Richon *et al.*, Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)) also completely inhibited the histone deacetylase activity of HDAC9-FLAG and HDAC9a-FLAG. The HDAC activity of HDAC9 and HDAC9a was about ten times lower than the deacetylase activity of HDAC4 when comparable amount of protein was used under conditions tested here.

HDAC9 and HDAC9a enzymatic activity was also determined through HDAC enzymatic assays using ³H-histones isolated from murine erythroleukemia cells as a substrate. This assay was performed essentially as described by Richon *et al.* (Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)). Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with ³H-histones overnight at 37°C. The reaction was stopped by the addition of 1M HCl/0.1 acetic acid. Released ³H-acetic acid was extracted with ethyl acetate and quantified by scintillation counting. For inhibition studies, the immunoprecipitated complexes were preincubated with the different HDAC inhibitors for 30 minutes at 4°C.

As shown in FIG. 8, HDAC9a-FLAG deacetylated ³H-acetyl-histones. SAHA, a potent HDAC inhibitor also completely inhibited the histone deacetylase activity of HDAC9a-FLAG. TSA also inhibited HDAC9a deacetylase activity. Similar results were obtained when HDAC9 was used as the enzyme source.

HDAC9 and HDAC9a repress MEF2-mediated transcription

The Xenopus homolog of HDRP, MITR, was identified as a MEF2 interacting transcriptional repressor (Sparrow *et al.*, EMBO J. 18:5085-5098(1999)) and mouse HDRP also interacts with and represses MEF2 mediated transcription (Zhang *et al.*, J. Biol. Chem. 276:35-39 (2001)). We first tested whether HDAC9-FLAG and HDAC9a-FLAG interact with MEF2. 293 cells were transfected with

vector, HDAC9-FLAG, or HDAC9a-FLAG. The cells were subsequently lysed and HDAC9-FLAG and HDAC9a-FLAG proteins were immunoprecipitated with anti-FLAG antibodies. Western blot analysis of the immunoprecipitated proteins was carried out, using anti-MEF-2 antibody to probe the blot. As shown in FIG. 9A, both HDAC9 and HDAC9a interacted with MEF2 in 293T cells.

It was then determined whether HDAC9 and HDAC9a repress MEF2-mediated transcription. This determination was carried out as follows. The p3XMEF2-luciferase reporter gene (100 ng) and the vector pRL-TK (Promega) (5 ng) were co-transfected into 293T cells in the absence (pcDNA3 empty vector) or presence of MEF2C (100 ng of pCMV-MEF2C). HDAC9-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9; pFLAG-HDAC9 and HDAC9-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9 nucleotide, but are functionally equivalent) or HDAC9a-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9a; pFLAG-HDAC9a and HDAC9a-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9a nucleotide, but are functionally equivalent) was included in a subset of experimental groups with the MEF2C vector. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The cells were harvested 24 to 36 hours after transfection and the luciferase activities were measured using the Dual-Luciferase™ Reporter Assay System from Promega according to the manufacturer's instruction. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity (encoded by the pRL-TK vector), and the luciferase activity value for cells transfected with MEF2C alone was set at 1. MEF2C activated transcription over 30 times the basal level of transcription. As shown in FIG. 9B, HDAC9-FLAG and HDAC9a-FLAG repressed MEF2C mediated transcriptional activation in a dose-dependent manner and completely abolished the activation at the 100 ng dose for both HDAC9 and HDAC9a. The transcriptional repression effect of HDAC9 and HDAC9a on MEF2C mediated transcription was a specific effect since a co-transfected reporter gene for transfection efficiency containing a TK promoter was not repressed by HDAC9 or HDAC9a.

Described herein is the identification and characterization of a new class II HDAC, designated HDAC9. HDAC9 has several alternatively spliced isoforms,

one of which is the previously identified HDRP (Zhou *et al.*, Proc. Natl. Acad. Sci. USA 97:1056-1061 (2000)). HDAC9 and HDAC9a possess HDAC activity, which appears to have a lower specific enzymatic activity than HDAC4. While not wishing to be bound by any particular theory, it is possible that an essential co-factor is lost during immunoprecipitation or does not exist in 293T cells (for example, metastasis-associated protein 2 is essential for the assembly of a catalytically active HDAC1 (Zhang *et al.*, Genes Dev. 13:1924-1935 (1999)), the substrates used are not its natural substrate, or the FLAG tag which interferes with the folding of the protein.

10 Searching the human genome with the HDAC domain from either HDAC1 or HDAC9 identified a total of 10 HDACs in the presently completed human genome sequence, a number of which are schematically represented in FIG. 10. HDACs 1, 2, 3, 8, 4, 5, 6, 7, 9, and 9a all have HDAC domains. HDRP, which is also schematically depicted in FIG. 10, does not have a catalytic domain.

15 All references described herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with reference to preferred embodiment thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended
20 claims.

CLAIMS

What is claimed is:

- 5
1. An isolated or recombinant histone deacetylase polypeptide, said polypeptide selected from:
- 10
- a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and
- b) an isolated or recombinant polypeptide having at least 60% sequence identity with any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 15
2. The isolated or recombinant histone deacetylase polypeptide of Claim 1, said polypeptide selected from:
- a) a polypeptide consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 20
3. The isolated or recombinant histone deacetylase polypeptide of Claim 1, wherein said polypeptide is human.
4. An isolated nucleic acid molecule selected from the group:
- 25
- a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9;
- b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9
- c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or
- 30
- SEQ ID NO: 10;

- d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;
- 5 e) a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or
- 10 f) a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and
- g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.
- 15 5. The isolated nucleic acid molecule of Claim 4, said nucleic acid molecule consisting of the nucleic acid molecule selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.
- 20 6. The isolated nucleic acid molecule of Claim 4, wherein said nucleic acid molecule is human.
7. A vector comprising the isolated nucleic acid molecule of Claim 4.
- 25 8. A cell comprising the vector of Claim 7.
9. A cell comprising the isolated nucleic acid molecule of Claim 4.
10. A purified antibody that selectively binds a polypeptide of Claim 1.
- 30 11. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:

- a) contacting said nucleic acid molecule with a candidate compound under conditions suitable for expression; and
- b) assessing the level of expression of said nucleic acid molecule, wherein a candidate compound that increases or decreases expression of said nucleic acid molecule relative to a control is a compound that modulates expression of said nucleic acid molecule.
- 5
12. The method of Claim 11, wherein said method is carried out in a cell or animal.
- 10
13. The method of Claim 11, wherein said method is carried out in a cell free system.
14. A method of identifying a compound that modulates the enzymatic activity of the polypeptide of Claim 1, said method comprising the steps of:
- 15
- a) contacting said polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and
- b) assessing the enzymatic activity level of said polypeptide, wherein a candidate compound that increases or decreases the enzymatic activity level of said polypeptide relative to a control is a compound that modulates the enzymatic activity of said polypeptide.
- 20
15. The method of Claim 14, wherein said method is carried out in a cell or animal.
- 25
16. The method of Claim 14, wherein said method is carried out in a cell free system.
17. The method of Claim 14, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an
- 30

apoptotic disease binding agent, and a cell differentiation disease binding agent.

18. The method of Claim 17, wherein said candidate compound is an inhibitor.

5

19. The method of Claim 17, wherein said candidate compound is an activator.

20. A method of identifying a compound that modulates the transcriptional repression activity of the polypeptide of Claim 1, said method comprising the steps of:

10

- a) contacting said polypeptide with a candidate compound under conditions suitable for a transcriptional repression reaction; and
- b) assessing the transcriptional repression activity level of said polypeptide,

15

wherein a candidate compound that increases or decreases the transcriptional repression activity level of said polypeptide relative to a control is a compound that modulates the transcriptional repression activity of said polypeptide.

20 21. The method of Claim 20, wherein said method is carried out in a cell or animal.

22. The method of Claim 20, wherein said method is carried out in a cell free system.

25

23. The method of Claim 20, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent.

30

24. The method of Claim 23, wherein said candidate compound is an inhibitor.

25. The method of Claim 23, wherein said candidate compound is an activator.
26. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:
- 5 a) providing a nucleic acid molecule comprising a promoter region of said nucleic acid of Claim 4 or part of a promoter region of said nucleic acid of Claim 4 operably linked to a reporter gene;
- b) contacting said nucleic acid molecule or with a candidate compound; and
- 10 c) assessing the level of said reporter gene,
- wherein a candidate compound that increases or decreases expression of said reporter gene relative to a control is a compound that modulates expression of said nucleic acid molecule of Claim 4.
- 15 27. The method of Claim 26, wherein said method is carried out in a cell.
28. A method of identifying a polypeptide that interacts with a polypeptide of Claim 1 in a yeast two-hybrid system, said method comprising the steps of:
- 20 a) providing a first nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and said polypeptide of Claim 1;
- b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide;
- 25 c) contacting said first nucleic acid vector with said second nucleic acid vector in a yeast two-hybrid system; and
- d) assessing transcriptional activation in said yeast two-hybrid system, wherein an increase in transcriptional activation relative to a control indicates that the test polypeptide is a polypeptide that interacts with said
- 30 polypeptide of Claim 1.
29. A pharmaceutical composition comprising a polypeptide of Claim 1.

30. A method of diagnosing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject, said method comprising the steps of:
- 5 a) obtaining a sample from said subject; and
- b) assessing the level of activity or expression of said polypeptide of Claim 1 in said sample, or detecting the level of said nucleic acid molecule of Claim 4,
- 10 wherein if said level is increased relative to a control, then said subject has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and wherein if said level is decreased relative to a control, then said subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.
- 15 31. The method of Claim 30, wherein said level of activity or expression of said polypeptide of Claim 1 in said sample is measured using immunohistochemical techniques.
- 20 32. The method of Claim 30, wherein said level of said nucleic acid molecule of Claim 4 in said sample is measured using *in situ* hybridization techniques.
- 25 33. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 14.
- 30 34. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 20.

'1/173

FIG. 1A
FIG. 1B
FIG. 1C
FIG. 1D
FIG. 1E
FIG. 1F
FIG. 1G
FIG. 1H
FIG. 1I
FIG. 1J
FIG. 1K
FIG. 1L
FIG. 1M
FIG. 1N
FIG. 1O

FIG. 1

HDAC93186 bp Coding 151-3186

Exon 1

1 ggggaagaga ggcacagaca cagataggag aagggcacgg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctageagc ctgaagaact
101 ctaagccaga tgggtgggt ggcagagagc agctcttggc tcagcaaaaga ATGCACAGTA TGATCAGCTC AGTGGATGTG AAGTCAGAAG TTCTGTGGG
201 CCTGGAGCCC ATCTCACCCTT TAGACCTAAG GACAGACCTC AGCATGATGA TGCCCGTGGT GGACCCCTGT GTCCGTGAGA AGCAATTGCA GCAGGAATTAA
301 CTTCTTATCC AGCAGCAGCA ACAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACAG GCAGCACCAG GCTCAGCTTC
401 AGGAGCATAT CAAGGAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAGGAGC AGAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG
501 GCATCGCAGA GAACAGCAGC TTCTCTCTCT CAGAGGCCAA GATAGAGGAC GAGAAAGGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC
601 CTACTGACTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGTTA CACGGCTGCC CACCACACAT
701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAG GATGATTCC CCCTTCGAAA
801 AACTGCCCTT GAGCCCAACT TGAAGGTGG GTCCAGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GGCGGAAGGA TGGAAATGTT

FIG. 1A

2/173

8
901 GTCACTTCAT TCAAGAAGCG AATGTTTGAG GTGACAGAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCAGTTC ACCAAACAAT GGGCCAACTG
9
1001 GAAGTGTAC TGAATAATGAG ACTTCGGTTT TGCCCCCTAC CCCTCATGCC GAGCAAAATGG TTTCACAGCA AGCAATCTA ATTCAATGAAG ATTCCATGAA
9
1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCAG CTCAATGCTT CGAATTCAT CAAAGAAAG
10
1201 CAGAAGTGTG AGAGCGAGAC GCTTAGGCAA GGTGTTCCIC TGCTGGGCA GTATGGAGC AGCATCCGG CATCTCCAG CCACCCTCAT GTTACTTTAG
10
1301 AGGAAAGCC ACCCAACAGC AGCCACCAGG CTCTCCTGCA GCATTATTAA TTGAAGAAC AAATGCGACA GCAAAGCTT CTTGTAGCTG GTGGAGTTCC
3/173
1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATG CCCCCTCACA GACCCCTGAA CCGAACCCAGG
11
1501 TCTGCACCTT TGCTCAGAG CAGCTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCA TTCTTGAGA AGCAGAAACA ATACCAGAG CAGATCCACA
11
1601 TGAACAACT GCTTTCGAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG GGGGACCAGG CGATGCAGGA
12
1701 AGACAGAGCG CCCTCTAGT GCAACAGCAC TAGGAGCGAC ACCAGTGCTT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGT CAAGGAGGAA
12
1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGA GCAGGCTGCT TTATGCAAC AGCCTTTCCT GGAACCCAGG CACACACGTG

FIG. 1B

4/173

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTGCTCTC CAGGACTCAC TCCTCCCTG CTGCCTCTGT
2001 TTACCTCAC CCAGCAATGG ACGCCCCCT CCAGCTGGC TCIGCAACTG CAATTGCCCTA TGACCCCTTG ATGCTGAAC ACCAGTCCGT TTGTGGCAAT
2101 TCCACCACC ACCCTGAGCA TGCTGGAGCA ATACAGAGTA TCTGGTCAG ACTGCAAGAA CTGGGGCTGC TAAATAAATG TGAGCAAT CAAGTGGAA
2201 AAGCCAGCCT GGAGGAATA CAGCTTGTTT CACTCACTG TTGTATGGCA CCAACCCCT GGACGGACAG AAGCTGGACC CCAGGATACT
2301 CTAGGTGAT GACTCTCAA AGTTTTTTC CTCAATTACCT TCTGGTGGAC TTGGGGTGG CAGTGACACC ATTGGAATG AGTACACTC GTCCGGTGT
2401 GCACGATGG CTGTTGGCTG TGTATCGAG CTGGCTTCCA AAGTGGCTC AGGAGAGCTG AAGAAATGGT TTGCTGTGT GAGCCCCCT GGCCATCAG
2501 CTGAAGATC CACAGCCATG GGGTCTGT TTTTAAATC AGTTGCAAT ACCGCCAAT ACTTGAGACA CCACTAAAT ATAAGCAAGA TATTGATTGT
2601 AGATCTGGAT GTTACCATG GAAAGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACAT TCACTCCATC GCTATGATGA AGGAACTTT
2701 TTCCCTGGCA GTGGAGCCC AATGAGGTT GGAACAGGCC TTGGAGAAG GTACAATATA AATATTGCCT GGACAGGTGG CCTGATCCT CCCATGGGAG
2801 ATGTTGATTA CCTTGAAGCA TTCAGGacca TCGTGAAGCC TGTGGCCAAA GAGTTTGATC CAGACATGTT CTTAGTATCT GCTGATTTG ATGCATTGGA
2901 AGGCCACACC CTCCTCTAG GAGGTACAA AGTGACGGCA AAATGTTTG GTCAATTGAC GAAGCAATG ATACATTTG CTGATGGACG TGTGGTGTG
3001 GCTCTAGAAG GAGGACATGA TCTACAGCC ATCTGTGATG CATCAGAGC CTGTGTAAAT GCCCTTCTAG GAAATGAGCT GGAGCCACTT GCAGAAGATA
3101 TTCTCCACCA AAGCCGAAT ATGAATGCTG TTATTTCTTT ACAGAAGATC ATTGAATTC AAAGTATGTC TTTAAAGTTC TCTTAA

FIG. 1C

HDAC9a 3499 bp (Coding 151-2790)
Exon 1

1 ggggaagaga ggcacagaca cagataggag aagggcacgg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact

101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga ATGCACAGTA TGATCAGCTC AGTGGATGTG AAGTCAGAAG TTCTCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCGTGGT GGACCCCTGTT GTCCCTGAGA AGCAATTGCA GCAGGAATTA

301 CTTCTTATCC AGCAGCAGCA ACAAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACAGG GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAGGAACTT CTAGCCATAA AACAGCAACA AGAATCTCTA GAAAGGAGC AGAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCTCTCTCT CAGAGGCAAA GATAGAGGAC GAGAAAGGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC

5/173

FIG. 1D

5
601 CTACTGACTA ATACAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGTCTGGTA CACGGCTGCC CACCACACAT
701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCTTACAG TACACATTAC CAGGAGCACA AGATGCAAG GATGATTTC CCCTTCGAAA
801 AACTGCTCT GAGCCCAACT TGAAGGTGG GTCCAGTTA AACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GCGGAAGGA TGGAAATGTT
901 GTCACTTCAT TCAAGAAGC AATGTTTGG GTGACAGAAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCAGTTC ACCAAACAAT GGGCCAACTG
1001 GAAGTGTAC TGAANAATGAG ACTTCGGTTT TGCCCCCTAC CCTCATGCC GAGCAAAATG TTTCACAGCA AGCATTCTA ATTCATGAG ATTCCAAGAA
1101 CCTGCTAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGC TTCCGCGAGT GCCATCCCAG CTCATGCTT CGAATTCAT CAAAGAAAAG
1201 CAGAAGTGTG AGAGGCAGAC GCTTAGGCAA GGTGTTCTC TGCCCTGGCA GTATGGAGGC AGCATCCCG CATCTTCCAG CCACCTCAT GTTACTTTAG
1301 AGGGAAGCC ACCCAACAGC AGCCACCAG CTCCTCTGCA GCATTATTA TTGAAGAAC AAATGGACA GCAAAAGCTT CTTGTAGCTG GTGAGTTCC
1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATG CCCCCTGACA GACCCCTGAA CCGAACCCAG
1501 TCTGCACCTT TGCCTCAGAG CAGGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCA TTCTTGGACA AGCAGAACA ATACCAGAG CAGATCCACA

FIG. 1E

6/173

1601 TGAACAACT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGACTTCAG GGGGACCAGG CGATGCAGGA
1701 AGACAGAGCG CCCCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCCT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA
1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AGCCTTTCCT GGAACCCACG CACACACGTG
1901 CGCTCTCTGT GCGCCAGAGT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTGCTC CAGGACTCAC TCTTCCCCTG CTGCCCTCTT
2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATTCCTTA TGACCCCTTG ATGCTGAAAC ACCAGTGCCT TTGTGGCAAT
2101 TCCACCACCC ACCCTGAGCA TGCTGGACGA ATACAGAGTA TCTGGTACAG ACTGCAAGAA ACTGGGCTGC TAATAAATG TGAGCGAAT CAAGGTGGA
2201 AAGCCAGCCT GGAGGAATA CAGCTTGTTT CACTCAGCA TCTGTTGGA CCAACCCCTT GGACGGACAG AAGCTGGACC CCAGGATAC
2301 CCTAGTGAT GACTCTCAA AGTTTTCCT CTCATTACCT TGTGGTGGAC TTGGGGTGGC CAGTGACACC ATTGGAATG AGTACACTC GTCCGGTGT
2401 GCACCATGG CTGTGGCTG TGTATGAG CTGGCTTCCA AAGTGGCTC AGGAGAGTG AAGATGGGT TTGCTGTGT GAGGCCCTT GGCCATCAG
2501 CTGAGAATC CACGCCATG GGGTCTGCT TTTTATTC ACTTGCAAT ACCGCCAAT ACTTGAGAGA CCACTAAAT ATAAGCAAGA TATTGATGT

FIG. 1F

21
 2601 AGATCTGGAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTATTGCTG ACCCCAGCAT CCTGTACATT TCATCCATC GCTATGATGA AGGGAACTTT
 2701 TTCCCTGGCA GTGGAGCCCC AATGAGGTT CCGTTTATTT CTTTAGAGCC CCACITTTAT TTGTATCTTT CAGGTAATTG CATTGCATGA ttacccttaa
 STOP CODON
 22
 2801 tttttctgtc ctttgctggt gttttaatt acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa gtgcataacc cagagcactg
 2901 tttgtcaggg aagggtgggc tgatttgatg tgtttatttc aagagctccc atgtgcttgt tttcctctct tcttgcttcc ttccatttgc
 3001 tctcttctct gccacaccgt gtgtgtcttt ctcttcccag gttggaacag gccttggaga aggtataaat ataaatattg cctggacagg tggccttgat
 3101 cctcccatgg gagatgttga gtacctgaa gcattcagga ccactgtgaa gcctgtggcc aaagagtgtg atccagacat ggtcttagta tctgttggtat
 3201 ttgatgcatt ggaaggccac accctctctc taggagggtg caaagtgcag gcaaaatggt ttggtcattt gacgaagcaa ttgatgacat tggtgatgg
 3301 acgtgtggtg ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcatacga agcctgtgta atgccccttc taggaatga gctggagcca
 3401 cttgcagaag atattctcca ccaaagcccg aatatgaatg ctgttatttc ttacagaag atcattgaaa ttcaagtat gtctttaag ttctcttaa

FIG. 1G

9/173

>HDRP (deltaNLS)
1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca
51 cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaaact
101 ctaagccaga tgggtggct ggacgagagc agctcttggc tcagcaaaaga
151 atgcacagta tgatcagctc agtgatgtg agtcagaag ttctgtggg
201 cctggagccc atctcacctt tagacctaa gacagacctc aggatgatga
251 tgcccggtgt ggacctgtt gtccgtgaga agcaattgca gcaggaatta
301 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
351 gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
401 aggagcatat caaggaaact ctagccataa aacagcaaca agaactccta
451 gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
501 gcatcgcaga gaacagcagc ttctctctct cagaggcaaa gatagaggac
551 gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
601 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
651 ttccgtgagc cgccatccca agctctggtg cagggtgcc caccacacat
701 catggatca aagctctcca ccccttagtg gaacatctcc atctacaag
751 tacacattac caggagcaca agatgcaaa gatgatttc ccctcgaaa
801 aactgaatcc tcagtcagta gcagttctcc aggtcttgtt ccagttcac
851 caaacaatgg gccaaactgga agtgttactg aaatgagac ttcggttttg
901 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaata
951 tcatgaagat tccatgaacc tgctaagtct ttatacctct cctcttttg
1001 ccaacattac ctgggggctt cccgcagtgc catccagct caatgcttcg

FIG. 1H

10/173

1051 aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctgggcagt atggaggcag catccggca tcttccagcc
1151 accctcatgt tactttagag ggaagccac ccaacagcag ccaccaggct
1201 ctccctgcagc atttattatt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1251 tgtagctggt agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1301 cccctgaacc gaaccagtc tgcacctttg cctcagagca cgttggtca
1351 gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1401 accagcagca gatccacatg acaaaactgc ttgcgaaatc tattgaacaa
1451 ctgaagcaac caggcagtca cttgaggaa gcagagggaag agcttcaggg
1501 ggaccaggcg atgcaggaa acagagcgcc ctctagtggc aacagcacta
1551 ggagcgacag cagtgttgt gtggatgaca cactgggaca agttggggct
1601 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcatatcca
1651 ggaaatggaa tctggggagc aggctgcttt tatgcaacag gtaataggca
1701 aagatttagc tccaggattt gtaattaaag tcattatctg a
1751

FIG. 11

11/173

>HDAC9 (deltaNLS)
1 ggggaagaga ggcacagaca cagataggag aaggcacccg gctggagcca
51 ctgcaggac tgagggtttt tgcaacaaaa cctagcagc ctgaagaact
101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaaga
151 atgcacagta tgatcagctc agtggatgtg agtcagaag ttcctgtggg
201 cctggagccc atctcacctt tagacctaa gacagacctc aggatgatga
251 tgcccgtggg ggaccctgtt gtccgtgaga agcaattgca gcaggaatta
301 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
351 gttcagaaa cagcatgaga acttgacacg gcagcacccg gctcagcttc
401 aggagcatat caaggaaactt ctagccataa aacagcaaca agaactccta
451 gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
501 gcatcgcaga gaacagcagc ttctctctct cagaggcaaa gatagaggac
551 gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
601 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
651 ttccgtgagc cgccatccca agctctggta cagggtgcc caccacacat
701 cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag
751 tacacattac caggagcaca agatgcaaa gctgatttcc cccttcgaaa
801 aactgaatcc tcagtcagta gcagttctcc aggctctggt ccagttcac
851 caaacaatgg gccaaactgga agtgttactg aaatgagac ttcggttttg
901 cccctaccc ctcatgccga gcaaatgggt tcacagcaac gcattctaat
951 tcatgaagat tccatgaacc tgctaagtct ttataacctt ccttctttgc
1001 ccaacattac ctgggggctt cccgcagtgc catccagct caatgcttcg
1051 aattcactca aagaaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctgggcagt atggaggcag catccggca tttccagcc

FIG. 1J

12/173

1151 accctcatgt tactttagag ggaagccac ccaacagcag ccaccaggct-
1201 ctcccgagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtacct aaaaattgcc ccgtcacaga
1351 ccctgaacc gaaccagtc tgcaccttg cctcagagca cgttgggtca
1401 gctggtcatt caacagcaac accagcaatt ctgggagaag cagaagcaat
1451 accagcagca gatccacatg aaaaaactgc ttccgaaatc tattgaacaa
1501 ctgaagcaac caggcagtc ccttgaggaa gcagaggaag agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgcctgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701 ggaaatggaa tctggggagc aggtgcctt tatgcaaacag cctttccttg
1751 aaccacgca cacacgtgcg ctctctgtgc gccaaagctcc gctgggtgag
1801 gttggcatgg atggattaga gaaacacgt ctcgctcca ggactcactc
1851 ttcccctgct gcctctgtt tacctcacc agcaatggac cgccccctcc
1901 agcctggctc tgcaactgga attgcctatg accccttgat gctgaaacac
1951 cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051 agcgaattca aggtcgaaaa gccagcctgg aggaatatca gcttgttcat
2101 tctgaacatc actcactgtt gtatggcacc aacccctgg acggacagaa
2151 gctggacccc aggatactcc taggtgatga ctctcaaaag ttttttccct
2201 cattaccttg tggtgactt ggggtggaca gtgacaccat ttggaatgag
2251 ctacactcgt ccggtgctgc acgcattggc gtgggtgtg tcatcgagct
2301 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351 ggccccctgg ccatacagct gaagaatcca cagccatggg gttctgcttt
2401 ttttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat

FIG. 1K

13/173

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2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc  
2501 agcaggcctt ttatgctgac ccagcatedc tgtacatttc actccatcgc  
2551 tatgatgaag ggaacttttt ccctggcagt acaataaaa tattgcctgg acagggtggc  
2601 aacaggcctt ggagaagggg catgggagat gttgagtacc gtttgatcca gacatggctc tagtatctgc  
2651 ttgatcctcc tggaagcctg tggccaaaga gccacacccc catttgacga agcaattgat tcacagccat  
2701 gtgaagcctg gcatctggaag atgttttggg tctagaagga gtgtaaatgc ccttctagga aatgagctgg  
2751 tggatttgat tgacggcaaa tggatggcgtg gatggacgtg ctgtgatgca agccacttgc gaatgctgtt  
2801 tgacggcaaa atgttttggg tggatggcgtg gatggacgtg ctgtgatgca agccacttgc gaatgctgtt  
2851 gatggacgtg tggatggcgtg gatggacgtg ctgtgatgca agccacttgc gaatgctgtt  
2901 ctgtgatgca agccacttgc agaatatatt tgaattcaa agtatgtctt taaagtcttc  
2951 agccacttgc agaatatatt tgaattcaa agtatgtctt taaagtcttc  
3001 atttctttac agaatatatt tgaattcaa agtatgtctt taaagtcttc  
3051 ttaa
```

FIG. 1L

14/173

>HDAC9a (deltaNLS)
1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca
51 cttgcaggac tgagggtttt tgcaacaaaa ccttagcagc ctgaagaact
101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaaga
151 atgcacagta tgatcagctc agtggatgtg aagtcagaag ttccctgtggg
201 cctggagccc atctacott tagacctaa gacagacctc aggatgatga
251 tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaaatta
301 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
351 gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
401 aggagcatat caaggaactt ctagccataa aacagcaaca agaactccta
451 gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
501 gcctcgcaga gaacagcagc ttctctctct cagaggcaaa gatagaggac
551 gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
601 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
651 ttccgtgagc cgccatccca agctctggtg cacggctgcc caccacacat
701 cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag
751 tacacattac caggagcaca agatgcaaaag gatgatttcc cccttcgaaa
801 aactgaatcc tcagtcagta gcagttctcc aggtctggt ccagttcac
851 caaacaatgg gccaaactgga agtgttactg aaaatgagac ttcggttttg
901 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat
951 tcatgaagat tccatgaacc tgctaagtct ttatacctct ccttctttgc
1001 ccaacattac cttggggcctt cccgcagtgc catcccagct caatgcttcg
1051 aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctggggcagt atggaggcag catcccgga tcttcagcc
1151 accctcatgt tacttttagg ggaaagccac ccaacagcag ccaccaggct

FIG. 1M

15/173

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1201 ctccctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctgggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtacct agaggtgcc ccgtcacaga
1351 ccctgaacc gaaccagtc gaaccctttg tgcacctttg cctcagagca cgttggtca
1401 gctggtcatt caacagcaac accagcaatt ctggagaag cagaagcaat
1451 accagcagca gatccacatg acaaaactgc ttctgaaatc tattgaacaa
1501 ctgaagcaac caggcagtca cctgaggaa gcagaggaag agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgttgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701 ggaatggaa tctggggagc aggtgcttt tatgcaacag cctttcctgg
1751 aaccacgca cacacgtcg cctctgtgc gccaaactcc gctggctggc
1801 gttggcatgg atggattaga gaaacacagt ctgctcca ggactcactc
1851 tccccctgct gcctctgttt tacctcacc agcaatggac cgccccctcc
1901 agcctggctc tgcaactgga attgcctatg acccctgat gctgaaacac
1951 cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051 agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttgttcat
2101 tctgaacatc actcactgtt gtatggcacc aacccctgg acggacagaa
2151 gctggacccc aggatactcc taggtgatga ctctcaaaag ttttttccct
2201 cattaccttg tggaggactt ggggtggaca gtgacaccat ttggaatgag
2251 ctacactcgt ccggtgctgc acgcatggct gttggctgtg tcatcgagct
2301 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351 ggccccctgg ccatcacgt gaagaatcca cagccatggg gttctgcttt
2401 ttttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat

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FIG. 1N

16/173

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2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc
2501 agcaggccctt ttatgctgac ccagcatcc tgtacatttc actccatcgc
2551 tatgatgaag ggaacttttt cctggcagt ccagcccaa atgaggttcg
2601 gtttatttct ttagagcccc acttttattt gtatctttca ggtaattgca
2651 ttgcatgatt accctaatt ttcttgctct ttgctggtgt tttaaattac
2701 acgagatttac tgaattgtcc catgggacca agaaccagtg cagaacaagt
2751 gcataaacca gagcactgtt tgtcagggaa ggttgggctg atttgatgtg
2801 ttgttttgatg ttattttcaa gagctcccat gtgcttgttt tcctctcttc
2851 ttgcttttctt ccatttgctc tcttctctgc ccaccgtggt gtgtctttct
2901 ctccccaggt tggaaacagg cttggagaag ggtacaatat aaatatggcc
2951 tggacagggtg gccttgatcc tcccatggga gatgtgagt accttgaagc
3001 attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg
3051 tcttagtata tgctggattt gatgcattgg aaggccacac ccctcctcta
3101 ggaggggtaca aagtgcaggc aaaatgtttt ggtcatttga cgaagcaatt
3151 gatgacattg gctgatggac gtgtggtgtt ggctctagaa ggaggacatg
3201 atctcacagc catctgtgat gcatcagaag cctgtgtaaa tgcccttcta
3251 ggaaatgagc tggagccact tgcagaagat attctccacc aaagcccga
3301 tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt
3351 ctttaaaagt ctcttaa
```

FIG. 10

FIG. 2A
FIG. 2B
FIG. 2C
FIG. 2D
FIG. 2E

FIG. 2

>HDAC9 (1011 amino acids)
MHSMISSVDVKSEVPVGLPI SPLDLRTDLRMMPVDPVREKQLQQLLIQQQQQI
QKQLLIAEFQKHENLTRHQQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEVEERH
RREQQLPPLRGKDRGRERAVASTEYKQKLQEFLLSKSATKDTPTNGKNHVSRRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKTYTLPGAQDAKDDFPLRKTASEPNLKVRSRLKQKVAE
RRSSPLLRRKDGNVVTSFKKRMFEVTESVSSSSPGSGSPNNNGPTGSVTENETSVLP
PTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQHLLLKEQMRQQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLP RHRPLNRTQSAPLPQSTLAQLVIQQQHQQFL
EKQKQYQQQIHMNKLKLSIEQLKQPGSHLEEAEEEEELQDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVEEPVDSDEDAQIQEMESGEQA AFMQQPFLEPTHTRALSVRQA
PLA AVGMDGLEKHLVSRTHSSPAASVLPHPAMDRLPQPGSATGIA YDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHHSLLYGTNP LD
GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
GELKNGFAVVRPPCHHAAEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQA FYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNININIAWTGGLDPPMGDV
EYLEAFRTIVKPVAKFDPDMVLVSAGFDAL EGHTPPLGGYKVTA KCFGHLTKQLMTLA
DGRVVLAL EGGHDLTAICDASEACVNALLGNELEPLAEDILHQSPNMNAVISLQKIEI
QSM SLKFS

FIG. 2A

18/173

>HDAC9a (879 amino acids)
MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMMPVDPVREKQLQQLLLIQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTASEPNLKVRSRLKQKVAE
RRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSPGSPSPNNGPTGVTENETSVLP
PTPHAEQMVVSQQRILIHEDSMNLLSLYTSPLPNITLGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQHLLLEQMRQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQSTLAQLVIOQQHQQFL
EKQKQYQQQIHMNKLKLSKIEQLKQPGSHLEEAEEEEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVEEPVDSDEDAQIQEMESGEQAAMQPPFLEPTHTTRALSVRQA
PLAAVGM DGLEKHLVSRTHSSPAASVLPHPAMDRPLQPGSATGIAYDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHSLLYGTNPLD
GQKLDPRILLGDDSQKFFSSLPCCGLGVDSDTIWNELHSSGAARMVAVGCVIELASKVAS
GELKNGFAVVVRPPGHHAEEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFYLYLSGNCIA

FIG. 2B

19/173

>HDAC9 (ANLS) (967 amino acids)
MHSMISSVDVKSEVPVGLPISPDLRLTDLRMMMPVDPVVRKQLQQLLELLLIQQQQQI
QKQLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQORILIHEDSMNLLSLYTSPLPNTLGLPAVPS
QLNASNSLKEKQKCEQTQLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQKLLVAGGVPLHPQSPPLATKERISPGIRGTHKLP RHRPLNRTQSAPLPQS
TLAQLVIQQHQHQQFLEKQKQYQQQIHMNKL LSKSIEQLKQPGSHLEEAEEEELOGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKKEPVDSEDAQIQEMESGEQA AFMQQP
FLEPTHTRALSVRQAPLA AVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLP CGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNI
NIAWTGGLDPPMGDVEYLEAFRTIVKPVAKFEFDPDMVLVSAGFDALEGHTPPLGGYKVT
AKCFGHLTKQLMTLADGRVVLALEGGHDLTAICDASEACVNALLGNELEPLAEDILHQ
PNMNAVISLQKIIIEIQMSLSLKFS

FIG. 2C

20/173

>HDAC9a (ANLs) (835 amino acids)
MHSMISSVDVKSEVPVGLPI SPLDLRTDLRMMMPVDPVREKQLQQLLELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVEERH
RREQQLPPLRGKDRGRERAVASTEYKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPLPNI TLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLP RHRPLNRTQSA PLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKL LSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAIQEMESGEQA AFMQQP
FLEPHTRALSVRQAPLA AVGMDGLEKHR LVSRT HSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCE RIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLP CGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHAAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDL DVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFY
LYLSGNCIA

FIG. 2D

21/173

>HDRPa (HDRP ΔNLS) (546 amino acids)
MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMMPVVDPVVREKQLQQELLIIQQQQQI
QKQLLIAEFQKHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYITLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNI'ITLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSI'PASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQOKLLVAGVPLHPQSP'LATKERISPGIRGTHKLP'RH'RP'LN'RTQSA'PI'PQS
TLAQLV'IQ'QH'Q'Q'FLEKQKQYQQQ'IH'MN'KL'SK'IEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGGEQA'AFMQQV
IGKDLAPGEV'IKVII

FIG. 2E

FIG. 3A
FIG. 3B
FIG. 3C

FIG. 3

FIG. 3A

HDRP	1	-----	MHSMISSVDVKSEVPVGLP	-----	ISPLDLRTDLRMMMP
HDAC9a	1	-----	MHSMISSVDVKSEVPVGLP	-----	ISPLDLRTDLRMMMP
HDAC9	1	-----	MHSMISSVDVKSEVPVGLP	-----	ISPLDLRTDLRMMMP
HDAC4	1	-----	MSSQSHPDGLSGRDQPVLLNPAR	-----	MHSMISSVDVKSEVPVGLP
HDRP	36	VVDPVVRKLOOELLII	OOOOIOKOLLIAEFQKOHENLTROHQAOL	OEHIK	-----
HDAC9a	36	VVDPVVRKLOOELLII	OOOOIOKOLLIAEFQKOHENLTROHQAOL	OEHIK	-----
HDAC9	36	VVDPVVRKLOOELLII	OOOOIOKOLLIAEFQKOHENLTROHQAOL	OEHIK	-----
HDAC4	61	VAFPAIRREQLLOELLAL	KQKQIQRIILIAEFQRIQHEQLSRQHEAQL	HEHIK	QOQOEMLA
HDRP	93	IKOOOELLEKEOKLEO	ROOEOEVERHRREOOLP	PLRGKDRGRERAVASTE	VKOKLOEFFLL
HDAC9a	93	IKOOOELLEKEOKLEO	ROOEOEVERHRREOOLP	PLRGKDRGRERAVASTE	VKOKLOEFFLL
HDAC9	93	IKOOOELLEKEOKLEO	ROOEOEVERHRREOOLP	PLRGKDRGRERAVASTE	VKOKLOEFFLL
HDAC4	121	IKHOQOELLEHQRIKLE	HRHQEOEIEKEQHRHQ	KLQOLKNNKEKKEJSA	TEVKMKLOEFFVL
HDRP	153	SKSATKDTPTNGKNHS	VSRHPKLWYTA	AAHHTSLDOSSPPLSGT	SPSYKYTLPGAQDAKDD
HDAC9a	153	SKSATKDTPTNGKNHS	VSRHPKLWYTA	AAHHTSLDOSSPPLSGT	SPSYKYTLPGAQDAKDD
HDAC9	153	SKSATKDTPTNGKNHS	VSRHPKLWYTA	AAHHTSLDOSSPPLSGT	SPSYKYTLPGAQDAKDD
HDAC4	181	NK- -KKALAHRNINHC	ISDPRWYCKTQHS	SLSDOSSPQSGVST	SYNHPVLGMYDAKDD
HDRP	213	FPLRKTASEP	NLKVRSLKOKVA	ERRSSPLLRKDG	GNVVTSEFKRMFEVTESSSSSPG
HDAC9a	213	FPLRKTASEP	NLKVRSLKOKVA	ERRSSPLLRKDG	GNVVTSEFKRMFEVTESSSSSPG
HDAC9	213	FPLRKTASEP	NLKVRSLKOKVA	ERRSSPLLRKDG	GNVVTSEFKRMFEVTESSSSSPG
HDAC4	239	FPLRKTASEP	NLKVRSLKOKVA	ERRSSPLLRKDG	PNVTALIKRPLDVTDAQSS-APG

23/173

HDRP	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTSPLPNITL
HDAC9a	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTSPLPNITL
HDAC9	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTSPLPNITL
HDAC4	298	SGPSSPNNSSGS	VSAENGIAPAVPS	IPAEITSLAHR-LV	AREGSAAPLFL	LYTSPSLPNITL
HDRP	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGYGGSI	PASSSSHPHVT	LEGKPPNSSH
HDAC9a	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGYGGSI	PASSSSHPHVT	LEGKPPNSSH
HDAC9	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGYGGSI	PASSSSHPHVT	LEGKPPNSSH
HDAC4	357	GLPATGPSAGT	AGQQ-DIERLTL	PALQORLSLFFG	THLTPYLSIS-	-PIERDG--GAAH
HDRP	393	OALLQHLLLLKE	OMROOKLLVAGG	--VPLHPOSPLAT	KERISPGIRGTH	KLPRHRPLNRTO
HDAC9a	393	OALLQHLLLLKE	OMROOKLLVAGG	--VPLHPOSPLAT	KERISPGIRGTH	KLPRHRPLNRTO
HDAC9	393	OALLQHLLLLKE	OMROOKLLVAGG	--VPLHPOSPLAT	KERISPGIRGTH	KLPRHRPLNRTO
HDAC4	411	SPLLQHMMVLL	EQPPAQAPLVT	GLGALPLHAQS-L	VGADRVSPL--	SIHKLROHRPLGRIO
HDRP	451	SAPLPQ--STLA	QOLVIOOOHOO	FELEKOKO--	YOOOIHMNKL	LSKSIEOLKOPGSHLEAE
HDAC9a	451	SAPLPQ--STLA	QOLVIOOOHOO	FELEKOKO--	YOOOIHMNKL	LSKSIEOLKOPGSHLEAE
HDAC9	451	SAPLPQ--STLA	QOLVIOOOHOO	FELEKOKO--	YOOOIHMNKL	LSKSIEOLKOPGSHLEAE
HDAC4	467	SAPLPQNAQA	LIQOLVIOOOH	OOFELEKOKQ	QFQOOQLQMN	KIIPKPSIPEPARQPEISHFEEIE
HDRP	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDDTL	GOVGAVKVKEE	PVDSDEDAOIOEMES
HDAC9a	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDDTL	GOVGAVKVKEE	PVDSDEDAOIOEMES
HDAC9	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDDTL	GOVGAVKVKEE	PVDSDEDAOIOEMES
HDAC4	527	EELIREHQALL	DEPYLDRLP	GQKEAHAQAGV	QVKQEPLES	DEEEAEPPREVEIPGQRQPSIEQ
HDRP	566	GEQAAFMQO	OVIGKDLAPGF	VIKVI I-----	-----	-----
HDAC9a	566	GEQAAFMQO	OVIGKDLAPGF	VIKVI I-----	-----	-----
HDAC9	566	GEQAAFMQO	OVIGKDLAPGF	VIKVI I-----	-----	-----
HDAC4	587	ELLFRQQA	LLLEQORITH	QLRNYQASMEAA	GIPVSFGCHRP	ISRAQSSPASATFFIVSVQIEP

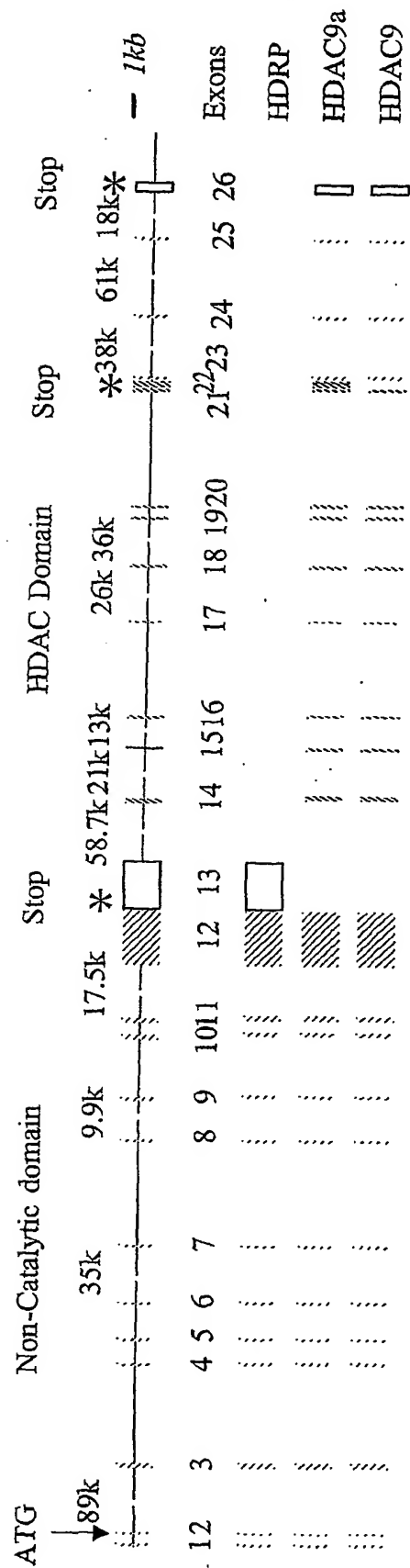
FIG. 3B

24/173

HD RP	626	PLQPGSATG	IA YD P L M L K H O C V C G N S T T H P E H A G R I O S I W S R L O E T G L L N K C E R I O G R K A
HD AC9a	626	PLQPGSATG	IA YD P L M L K H O C V C G N S T T H P E H A G R I O S I W S R L O E T G L L N K C E R I O G R K A
HD AC9	647	ETKPRFT	TIGLVYDTILMLKHOC TCGSSSSHP E H A G R I O S I W S R L O E T G L R G K C E I R G R K A
HD AC4			
HD RP	686	SLEETIO	L V H S E H S L L Y G T N P L D G O K L D P R I L L G D D S O K F F S S L P C G G L G V D S D T I W N E L
HD AC9a	686	SLEETIO	L V H S E H S L L Y G T N P L D G O K L D P R I L L G D D S O K F F S S L P C G G L G V D S D T I W N E L
HD AC9	707	TLEELIO	TVHSEAH T L L Y G T N P L N R O K L D S K L L G S I A S V E V R - L P C G G V G V D S D T I W N E V
HD AC4			
HD RP	746	HSSGAAR	MAVGC V I E L A S K V A S G E L K N G F A V V R P P G H H A E E S T A M G F C F F N S V A I T A K Y L
HD AC9a	746	HSSGAAR	MAVGC V I E L A S K V A S G E L K N G F A V V R P P G H H A E E S T A M G F C F F N S V A I T A K Y L
HD AC9	766	HSAGAARI	DAVGC V I E L V F K V A T G E L K N G F A V V R P P G H H A E E S T P M G F C F F N S V A V A A K I L
HD AC4			
HD RP	806	RDOLNIS	K I L I V D L D V H H G N G T O O A F Y A D P S I L Y I S L H R Y D E G N F F P G S G A P N E V R F I S L
HD AC9a	806	RDOLNIS	K I L I V D L D V H H G N G T O O A F Y A D P S I L Y I S L H R Y D E G N F F P G S G A P N E V R F I S L
HD AC9	826	QORLSV	S K I L I V D W D V H H G N G T O O A F Y S D P S V L Y M S L H R Y D D G N F F P G S G A P D E V G T G P C
HD AC4			
HD RP	866	EPHEYL	Y L S G N C I T A
HD AC9a	866	EGYNIN	I A M T G G L D P P M G D V E Y L E A F R T I V K H V A K E F D P D M V L V S A G F D A I E G H T P P L G G
HD AC9	886	VGENVN	M A F T G G L D P P M G D A E Y L A A F R T I V M E I A S E F A P D M V L V S G G F D A V E G H P T P L G G
HD AC4			
HD RP	926	YKVTAK	CFGHLTKOLM T L A D G R V V I A L E G G H D L T A I C D A S E A C V N A L L G N E L E P L A E D I L
HD AC9a	946	YNLSAR	CFGYLT K O L M G L A G G R I V I A L E G G H D L T A I C D A S E A C V S A L L G N E L D P L P E K V L
HD AC9			
HD AC4			
HD RP	986	HQSPNM	NAV I S I O K I I E I O S M S I K F S
HD AC9a	1006	QQR	ENANAV R S M E K V M E I H S K Y W R C L Q R T T S T A G R S L I E A Q T C E N E E A E T V T A M A S L S V G
HD AC9			
HD AC4			
HD RP	1066	VKPAEK	RPDEEP MEEEPPL
HD AC9a			
HD AC9			
HD AC4			

FIG. 3C

FIG. 3C



25/173

FIG. 4

FIG. 5A
FIG. 5B
FIG. 5C
FIG. 5D

FIG. 5

26/173

1 /¹ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa
ccctagcagc ctgaagaact

101 ctaagccag/²a tggggtggct ggacgagagc agctcttggc tcagcaaaaga ATGCACAGTA TGATCAGCTC AGT/³GGATGTG
AAGTCAGAAG TTCCTGTGGG

201 CCTGGAGCCC ATCTCACCIT TAGACCTAAG GACAGACCCTC AGGATGATGA TGCCCCGTGGT GGACCCCTGTT GTCCGTGAGA
AGCAATTGCA GCAGGAATTA

301 CTTCCTTATCC AGCAGCAGCA ACAATTCAG AACAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTCACACG
GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAAG/⁴GAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAAGGAGC AGAAACTGGA GCAGCAGAGG
CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCTCTCTCT CAGAGGGCAAA GATAGAGGAC GAGAAAG /⁵GGC AGTGGCAAGT ACAGAAGTAA
AGCAGAAGCT TCAAGAGTTC

601 CTA CTGTGAGTA AATCAGCAAC GAAACACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGA
CAGG/⁶GCTGCC CACCACACAT

701 CATTTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG
GATGATTCC CCCTTCGAAA

FIG. 5A

27/173

801 AACT/GCCTCT GAGCCCAACT TGAAGGTGCG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA
GGCGGAAGGA TGGAAATGTT

901 GTCACCTTCAT TCAAGAAGCG AATGTTTGAG GTGACAG /⁸AAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCAGTTT
ACCAACAAT GGGCCHACTG

1001 GAAGTGTAC TGAAAATGAG ACTTCGGTTT TGCCCCCTAC CCTTCATGCC GAG /⁹CAATGG TTTCACAGCA ACGCATTCTA
ATTGATGAG ATTCCATGAA

1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGGAGT GCCATCCCAG CTC AATG /¹⁰CTT
CGAATTCAT CAAAGAAAAG

1201 CAGAAGTGTG AGAGCGAGAC GCTTAGGCA GGTCTTCTC TGCCTTGGCA GTATGGAGC AGCATCCCCG CATCTTCCAG
CCACCTCAT GTTACTTTAG

1301 AGGGAAGCC ACCCAACAGC AGCCACCAGG CTCCTCTGCA GCATTTATTA TTGAAAGAAC AATGCGACA GCAAAAGCTT
CTTGAGCTG /¹¹ GTGGAGTTCC

1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCCTCACA
GACCCCTGAA CCGAACCAG

1501 TCTGCACCTT TGCCTCAGAG CAGGTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA
ATACCAGCAG CAGATCCACA

1601 TGAACAAA /¹²CT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG
GGGACCAGG CGATGCAGGA

FIG. 5B

28/173

1701 AGACAGAGCG CCTCTAGTG GCAACAGCAC TAGGAGGGAC AGCAGTGCCT GTGTGGATGA CACACTGGGA CAAGTTGGGG
CTGTGAAGGT CAAGGAGAA

1801 CCACTGGACA GTGATGAAGA TGCTCAGATC CAGGAATGG AATCTGGGA GCAGGCTGCT TTTATGCAAC AG
/¹³GTAAATAGG CAAAGATTAA GCTCCAGGAT TTGTAATTAA AGTCATTATC TGA..... /¹⁴CCTTTCCT GGAACCCACG CACACACGTG

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTGCTCTC CAGGACTCAC
TCTTCCCCCTG CTGCCTCTGT

2001 TTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG /¹⁵GAAATTGCCCTA TGACCCCTTG ATGCTGAAAC
ACCAGTGGGT TTGTGGCAAT

2101 TCCACCACCC ACCCTGAGCA TGCTGGACGA ATACAGAGTA TCTGCTCAG ACTGCAAGAA ACTGGGCTGC TAAATAAATG
TGAG/¹⁶CGAATT CAAGTTCGAA

2201 AAGCCAGCCT GGAGGAATA CAGCTTGTTTC ATTCTGAACA TCACCTCCTG TTGTATGGCA CCAACCCCTT GGACGGACAG
AAGCTGGACC CCAGGATACT

2301 CCTAG/¹⁷GTGAT GACTCTCAAA AGTTTTTTTC CTCATTACCT TGTTGGGAC TTGGG/¹⁸GTGGA CAGTGACACC ATTTGGGATG
AGCTACACTC GTCCGGTGCT

2401 GCACGCATGG CTGTTGGCTG TGTCAATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGA /¹⁹ATGGGT TTGCTGTGTG
GAGGCCCTT GGCCATCAG

2501 CTGAAGAATC CACAGCCATG /²⁰GGGTTCTGCT TTTTAAATTC AGTTGCAATT ACCGCCAAT ACTTGAGAGA CCAACTAAAT
ATAAGCAAGA TATTGATTGT

FIG. 5C

2601 AGATCTG/²¹GAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCAGCAT CCTGTACATT TCACTCCATC
 GCTATGATGA AGGGAACTTT
 2701 TTCCCTGGCA GTGGAGCCCC AAATGAGG/²²TT CCGTTTATTT CTTTAGAGCC CCACTTTAT TTGTATCTTT CAGGTAATTG
CATTGCATGA ttacccttaa
 2801 ttttcttgtc ctttgctggc gttttaaat acacgagatt actgaattgt cccatggac caagaaccag tgcagaacaa
gtgcataacc cagagcactg
 2901 tttgtcaggg aaggttggc tgatttgatg tgbtttga tgbttattc aagagctccc atgtgcttgt tttcctctct
tcttgcttc ttccatttgc
 3001 tctcttctct gccaccgtg gtgtgtctt ctctcccag /²³gttggaacag gccttgaga aggtacaat ataaatattg
cctggacagg tggccttgat
 3101 cctcccatgg gagatgtga gtacctgaa gcattcag/²⁴ga ccactgtgaa gcctgtggc aaagagttg atccagacat
ggtcttaga tctgctggat
 3201 ttgatgcatt ggaaggccac accctctc taggaggta caaagtacg gcaaatg/²⁵tt ttggtcattt gacgaagcaa
ttgatgacat tggctgatgg
 3301 acgtgtgggt ttggctctag aaggaggaca tgatctaca gccatctgtg atgcatcaga agcctgtgta aatgcccttc
taggaaatga g/²⁶ctggagcca
 3401 cttgagaag atattctca ccaagccc aatatgaatg ctgttattc ttacagaag atcattgaa ttcaaagtat
gtctttaaag ttctcttaa....

29/173

FIG. 5D

30/173

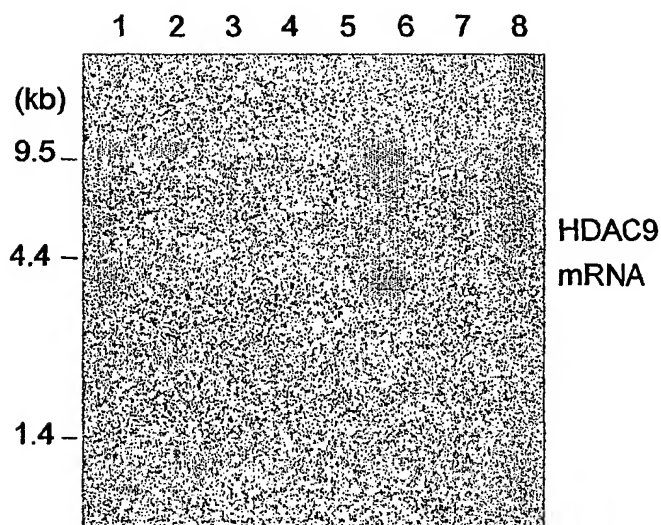


FIG. 6A

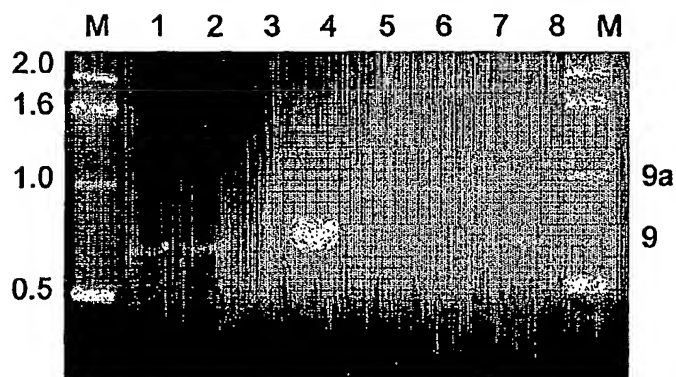


FIG. 6B

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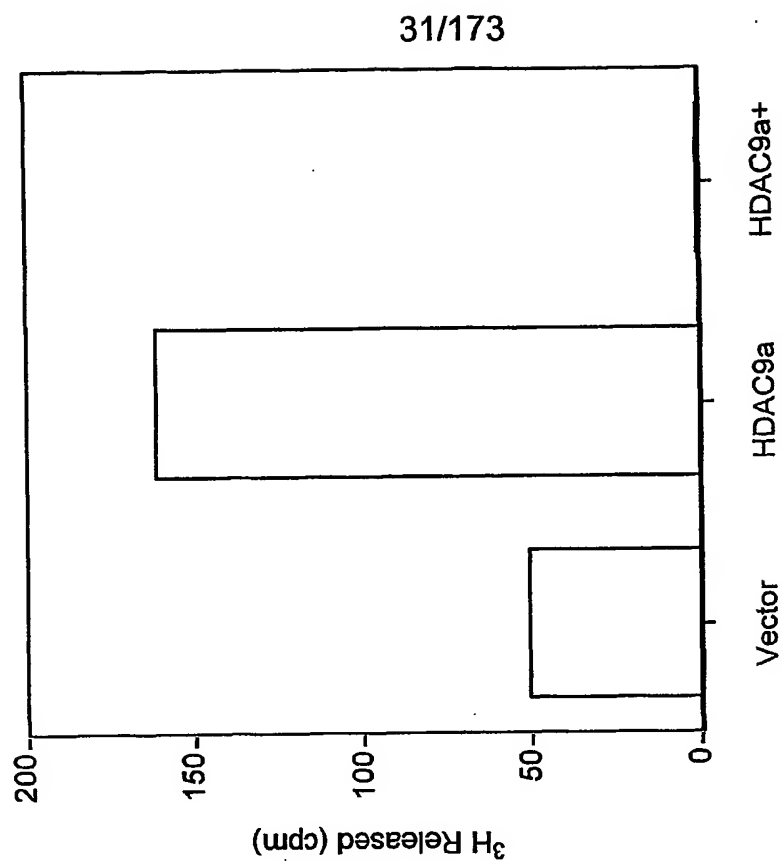


FIG. 8

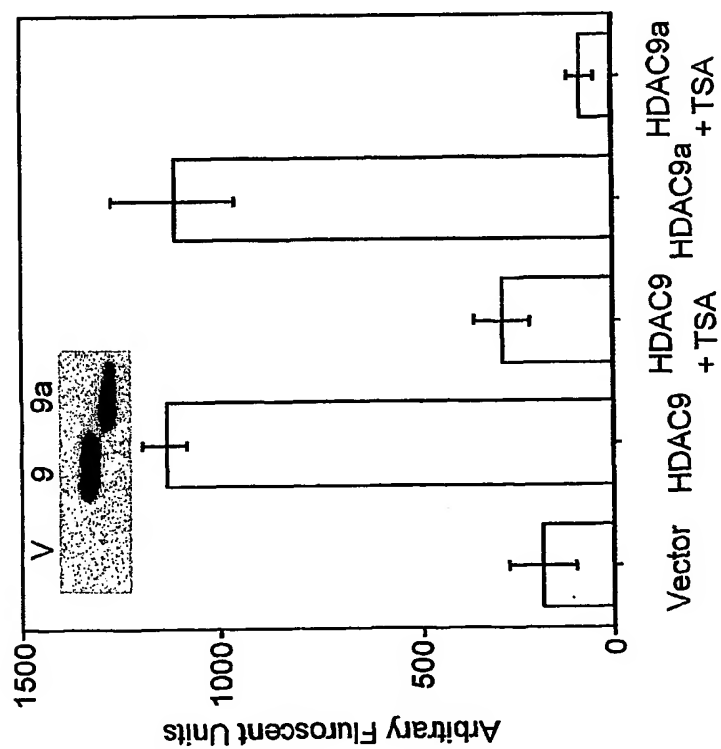


FIG. 7

FIG. 9A

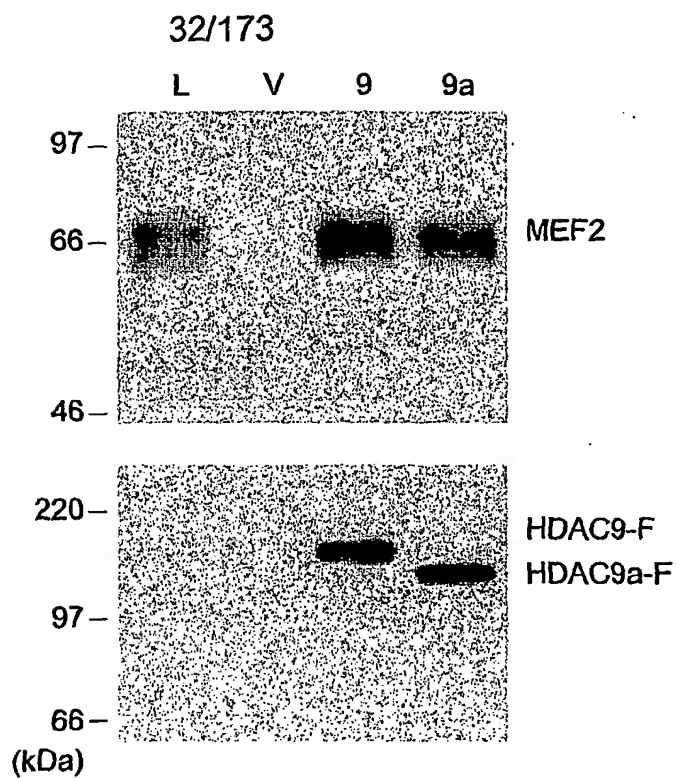
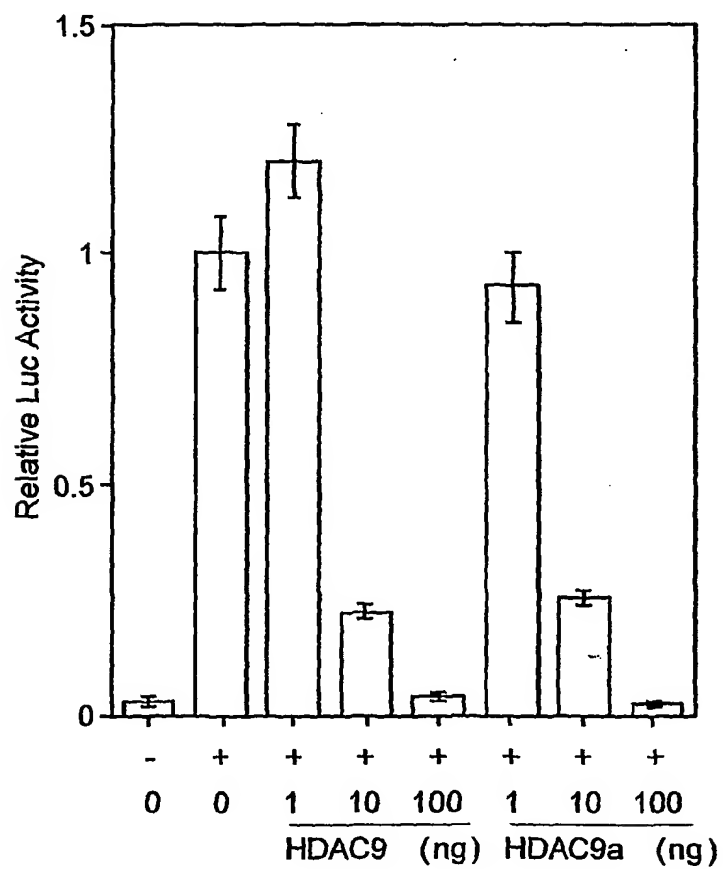


FIG. 9B



33/173

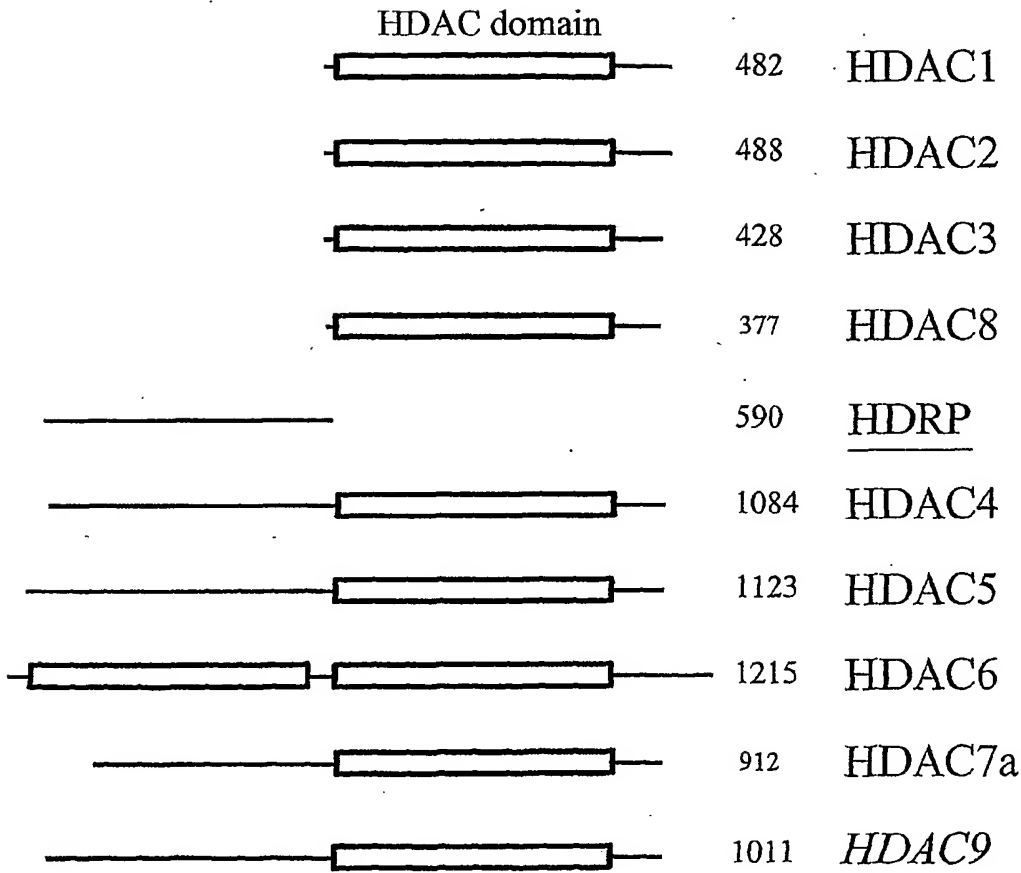


FIG. 10

FIG. 11A
FIG. 11B
FIG. 11C
FIG. 11D
FIG. 11E
FIG. 11F

FIG. 11

FIG. 11A

cccatcggcattcaggctgcgaactgttggaaggcgatcgggtggcctcttcgctattacgccagctggcgaaaggg
 ggatgtgctgcaaggcgattaagtgggtaacgccagggtttccagtcacgacgttgtaaacgacggccagtgccaagct
 gatctaataatattggccattagccatattattcattgggtatatagcataaataatattggcctattggccattgcatacgttgatcca
 tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgattattgactagttattaatagtaataatcag
 gggtcattagttcatagcccatatatggagttccgcgttacataacttacgtaaatggcccgctggcgaccgccagcgacccc
 ccgcccgttgacgtcaatagtgacgtatgttcccataagccaatagggactttccattgacgtcaatgggtggagtattacg

gtaactgccacttggcagtacatcaagtgtatcatatgccaaagtcgcccccctattgacgtcaatgacggtaaatggccgcct
 agcattatgccagtacatgaccttacggaggttctacttggcagtagacatctacgtattagtcacgtctattaccatgggtgatgcg
 gtttggcagtacaccaatggcgtgtagcgggttgactacgggatttccaagtctccaccattgacgtcaatgggaggt
 tgtttggcaccaaaatcaacgggactttccaaaatgtcgaataacccccggcgttgacgcaaatggcggtagcggtgtacg
 gtgggagggtctatataagcagagctcgttttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatc
 (EcoRV)
acc

35/173

ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAAGTTCCCTGTGGG
 CCTGGAGCCCATCTCACCTTTAGACCTAAGGACAGACCTCAGGATGATGA
 TGCCCCGTGGTGACCCCTGTTGTCCGTGAGAAGCAATTGCAGCAGGAATTA
 CTTCTTATCCAGCAGCAGCAACAATCCAGAAGCAGCTTCTGTATAGCAGA
 GTTTCAGAAACAGCATGAGAACTTGACACGGCAGCACCCAGGCTCAGCTTC
 AGGAGCATATCAAGGAACTTCTAGCCATAAACAAGCAACAAGAACTCCTA
 GAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAAACAGGAAAGTAGAGAG
 GCATCGCAGAGAACAGCAGCTTCTCCTCTCAGAGGCAAGATAGAGGAC
 GAGAAAGGCGAGTGGCAAGTACAGAAAGTAAAGCAGAAAGCTTCAAGAGTTC
 CTA CTGAGTAAATCAGCAACGAAAGACACTCCAACTAATGGAAAAATCA
 TTCCGTGAGCCGCATCCCAAGCTCTGGTACACGGCTGCCACACACAT
 CATTGGATCAAGCTCTCCACCCCTTAGTGGAACATCTCCATCCTACAAG

FIG. 11B

36/173

TACACATTACCAGGAGCACAGATGCAAGAGATGATTTCCCCCTTCGAAA
AACTGCCCTGTAGCCCAACTTGAAGTGCCTCAGGTTAAAAACAGAAAG
TGGCAGAGAGAGAACAGCCCTTACTCAGGCGAAGGATGGAAATGTT
GTCACTTCATTCAAGAACGGAATGTTTGAGGTGACAGAAATCCTCAGTCAG
TAGCAGTTCTCCAGGCTCTGGTCCAGTTCACCAAAACAATGGGCCAACTG
GAAGTGTTACTGAAAATGAGACTTCGGTTTTGCCCTTACCCCTCATGCC
GAGCAAAATGGTTTTCACAGCAACGCAATCTAAATTCATGAAGATTCATGAA
CCTGCTAAGTCTTTATACCTCTCCTTCTTTGCCCAACATTAACCTTGGGGC
TTCCCGCAGTGCCATCCCAGCTCAATGCTTCGAATTCACCTCAAGAAAAG
CAGAAAGTGTGAGACGCAGACGCTTAGGCAAGGTGTTCTCTGCTGCCCTGGGCA
GTATGGAGGCAGCATCCCGGCATCTTCCAGCCACCTCATGTACTTTAG
AGGAAAGCCACCCACAGCAGCCACAGGCTCTCCTGCAGCATTTATTA
TTGAAAGAACAAATGCGACAGCAAAAAGCTTCTTGTAGCTGGTGGAGTTCC
CTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAAATTCACCTGGCA
TTAGAGGTACCCACAAATTGCCCGTCAAGACCCCTGAACCGAACCCAG
TCTGCACCTTTGCCCTCAGAGCACGTTGGCTCAGCTGGTCAATTCACACAGCA
ACACAGCAATCTTGGAGAACGAGAACCAATACCAAGCAGCAGATCCACA
TGAACAAACTGCTTTTCGAAATCTATTGAACAACTGAAGCAACAGGCAGT
CACCTTGAGGAAGCAGAGGAAGAGCTTCAGGGGGACCAAGCGATGCAGGA
AGACAGAGCGCCCTCTAGTGGCAACAGCACTAGGAGCGACAGCAGTGCTT
GTGTGGATGACACACTGGGACAAAGTTGGGGCTGTGAAGGTCAAGGAGGAA
CCAGTGGACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGGA
GCAGGCTGCTTTTATGCAACAGCCTTCTCTGGAACCCACGCACACACGTG
CGCTCTCTGTGCGCCAAAGCTCCGCTGGCTGGCTTGGCATGGATGGATTA

FIG. 11C

37/173

GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCTGCTGCCCTCTGT
TTTACCTCACCAGCAATGGACCGCCCCCTCCAGCCTGGCTCTGCAACTG
GAATTGCCCTATGACCCCTTGATGCTGAAACACCAGTGCCTTTGTGGCAAT
TCCACCACCACCCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACG
ACTGCAAGAAACTGGGCTGCTAAATAAATGTGAGCGAAATTCAAGGTCGAA
AAGCCAGCCTGGAGGAAATACAGCTTGTTTCTGAAACATCACTCACTG
TTGTATGGACCAACCCCTGGACGGACAGAAAGCTGGACCCAGGATACT
CCTAGGTGATGACTCTCAAAAGTTTTTTTCTCTATTACCTTGTGGTGGAC
TTGGGGTGGACAGTGACACCAATTTGGAATGAGCTACACTCGTCCGGTGCT
GCACGCATGGCTGTTGGCTGTGTCTCATCGAGCTGGCTTCCAAAGTGGCCTC
AGGAGAGCTGAAGAAATGGGTTTGCTGTTGTGAGGCCCCCTGGCCATCACG
CTGAAGAAATCCACAGCCAATGGGGTCTGCTTTTAAATTGAGTTGCAATT
ACCGCCAAATACTTGAGAGACCAACTAAATAATAAGCAAGATAATTGATTGT
AGATCTGGATGTTTACCATGGAAACGGTACCAGCAGGCCTTTTATGCTG
ACCCAGCATCCTGTACATTTCACTCCATCCGCTATGATGAAGGAACTTT
TTCCCTGGCAGTGGAGCCCCAAATGAGGTTGGAAACAGGCCCTTGGAGAAGG
GTACAATATAAATATTGCTGGACAGGTGGCCTTGATCCTCCCATGGGAG
ATGTTGAGTACCTTGAAAGCATTCAGGAccaTCGTGAAGCCTGTGGCCAAA
GAGTTTGATCCAGACATGGTCTTAGTATCTGCTGGATTTGATGCATTGGA
AGGCCACACCCCTCCTAGGAGGTACAAAGTGACGGCAAAATGTTTGTG
GTCATTTGACGAAGCAATTGATGACATTGGCTGATGGACGTTGTGTGTG
GCTCTAGAAGGAGGACATGATCTCACAGCCATCTGTGATGCATCAGAAGC
CTGTGTAATGCCCTTCTAGGAAATGAGCTGAGCCACTTGCAGAAAGATA
TTCTCCACCAAGCCCCGAATATGAATGCTGTTATTCTTTTACAGAAGATC
ATTGAAATTCAAAAGTATGTCTTTTAAAGTTCTCT

FIG. 11D

FIG. 11E

[illegible]

39/173

FIG. 11F

40/173

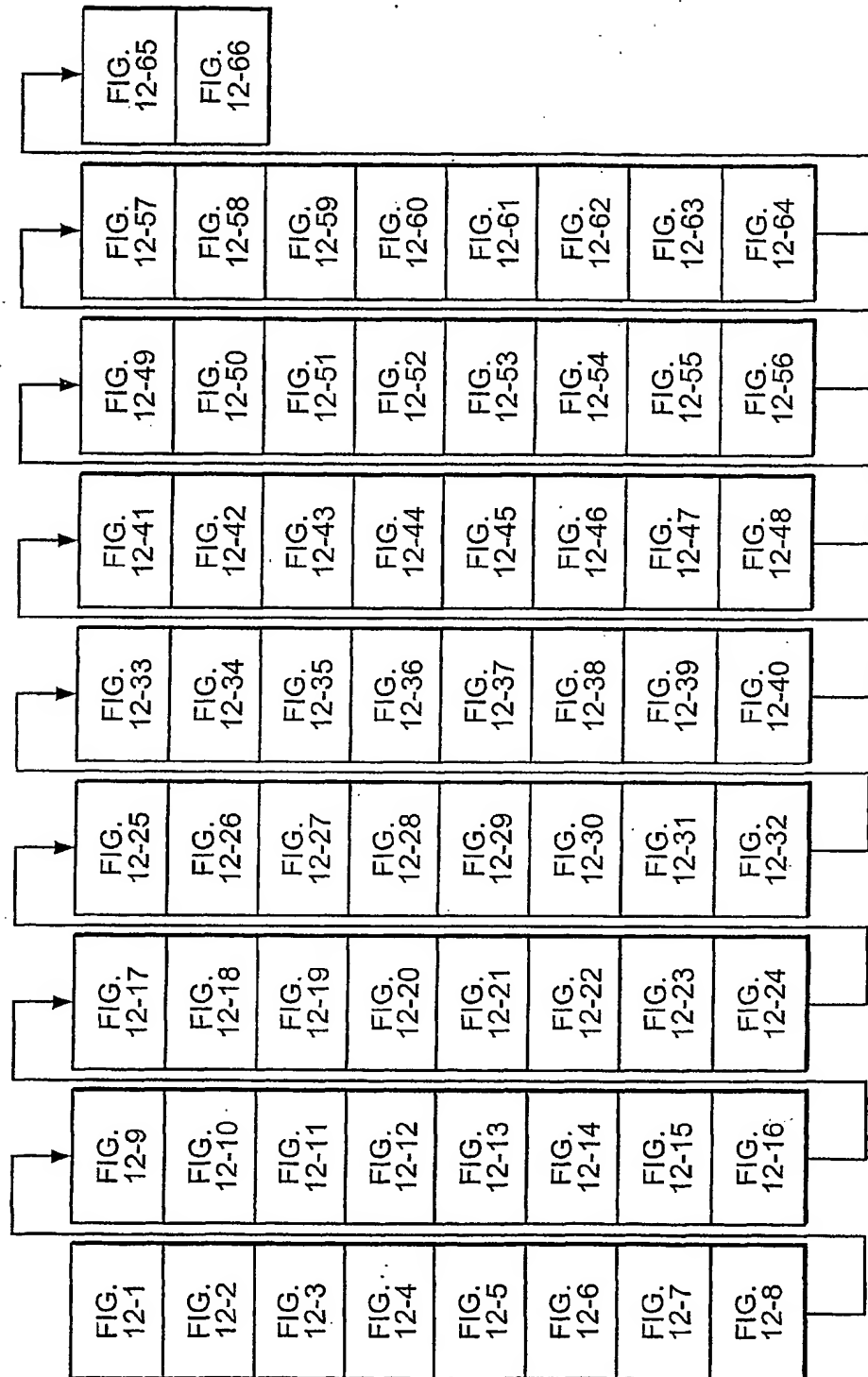


FIG. 12

pFLAG-CMV-5b-HDAC9

7699 base pairs

Graphic map | Table by enzyme name

cccatcgcattcaggctgcgcaactgttgggaaggcgatcggtgcgggcctcttcgctattacgccagctgg base pairs gggtaagcggtaagtcgcgacggttgacaaccccttcccgcctagccacgcccggagaagcgataatgcggtcgacc 1 to 75	AviII	BstMCI			
	BglI	PvuI	BsiEI	EcoRI	MspAII
	FspI	BsaOI		Eam1104I	PvuII
41/173	Acc16I	BspCI		Ksp632I	NspBII
		Bsh1285I			
		Ple19I			

cgaagggggatgtgctgcaaggcgattaaagtgggtaacgcccagggtttcccagtcacgacgttgtaaacg
base pairs
gctttccccctacacgacgttccgcctaattcaaccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150

FIG. 12-1

42/173

	MSCI	
	CfrI	
	SspI MluNI	
EaeI		
acggccagtgccaagctgatctaataatcaataattggccattagccataattattcattggttatatagcataaaatcaa		
base pairs		
tgccgggtcacgggttcgactagattagttataaacgggtaatcgggtataataagtaaccaataatatcgtatttagtt		
151 to 225		
CfrI	EaeI	
	Bali	
	MSCI	
	MluNI	
SspI EaeI BsrDI	SspBI	
	Bsp1407I	
tattgggtattggccattgcatacgttggtatccataatcgcataatgtacatttatattgggtcatgtccaaacatt		
base pairs		
ataaccgataaacgggtaacgtatgcaacatagggtatagttatatcatgtgtaataataaccgagtagcaggttgtaa		
226 to 300		
CfrI	BsrGI	
	Bali	

FIG. 12-2

HincII VspI
 SpeI PshBI
 accgccatgttgacattgattattgactagttattaatagtaataatcaattacggggtcatttagttcatagcccata
 base pairs
 tggcggtaacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatacaagtatcgggtat
 301 to 375
 HindII AclNI AsnI
 AseI

43/173

HinII BstMCI
 BsaOI
 BglI
 tatggagttccggttacataacttacggtaaatggcccgccctggcgaccgccccagcgacccccgcccgttgacg
 base pairs
 atacctcaaggcgcaatgtattgaatgccatttaccggcggaaccgctggcggggtcgctggggggcggaactgc
 376 to 450
 Bsh1285I HindII
 BsiEI

FIG. 12-3

AatII
 BbiII
 tcaatagtgacgtatgttcccatagtaacgccaataggactttccattgacgtcaatgggtggagtatttacgg
 base pairs
 agttatcactgcatacaagggtatcattgcggttatccctgaaaaggttaactgcagttacccacctcataaatgcc
 451 to 525
 Hsp92I
 BbiII
 HinII
 AcyI AatII
 44/173
 Msp17I
 BsaHI
 Hsp92I
 BglI
 NdeI
 taaactgcccacttggcagtagtatcaagtgtatcatatgccaaagtcgccccctattgacgtcaatgacggtaaa
 base pairs
 atttgacgggtgaaccgtcatgtagttcacatagtagtgcaggggggataaactgcagttactgccattt
 526 to 600
 BbiII
 HinII
 AcyI AatII
 Msp17I
 BsaHI
 Hsp92I
 FauNDI

FIG. 12-4

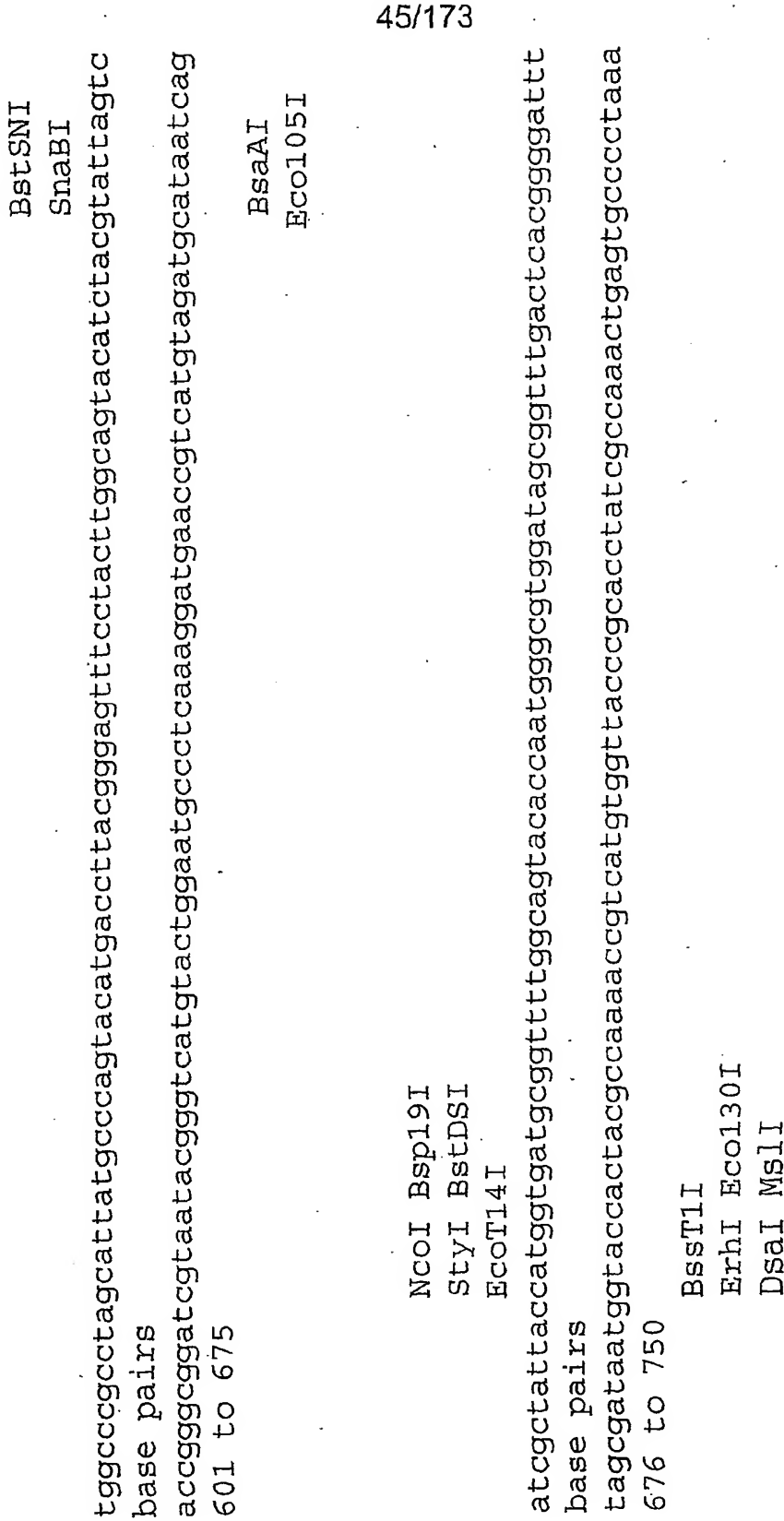


FIG. 12-5

BblII
 HinfI
 AclI AatII
 AccB1I
 BshNI
 ccaagtctccacccattgacgtcaatgggagttgttttggcaccaaaaatcaacgggactttccaaaatgtcgt
 base pairs
 ggttcagaggtgggtaactgcagttaccctcaacaaaaccgtggttttagttgcccctgaaagggttttacagca
 751 to 825
 Msp17I
 BsaHI
 Hsp92I
 BanI
 Eco64I
 46/173
 HincII
 BaniI
 Eco24I
 EcoICRI
 aataacccccccgttgacgcgcaaatgggcggttaggcgtgtacggtgggaggtctatataaagcagagctcgttta
 base pairs
 ttattgggcggggcaactgcggtttaccgcccatccgcacatgccaccctccagatatattcgtctcgagcaaat
 826 to 900
 HindII
 Ecl136II
 SacI

FIG. 12-6

FriOI
 SstI
 BsiHKA I
 Bbv12I
 AcsI
 ApoI
 AspHI
 gtgaaccgtcagaattcaagcttgccgcagatctatcgatctgcaggatatcaccatgcacagtatgacg
 base pairs
 cacttggcagctcttaagttcgaaacggcgctctagatagtagacgtcctatagtggtacgtgtcactactagtc
 901 to 975
 Psp124BI
 EcoRI
 Alw21I
 47/173
 EaeI
 CfrI
 NotI
 BglII
 BscI
 XhoII
 BspXI
 BstSFI
 BseCI
 ClaI
 Bsp106I
 BclI
 Ksp22I
 CviOI
 Eco24I
 BpmI
 CvnI
 AocI
 Bsu36I
 Bsu36I
 ctcagtggtgtgaagtcagaagttcctgtgggctggagcccatctcacctttagaccctaaggacagacctcag
 base pairs
 gagtcacctacacttcagttctcaaggacacccggacccctcggttagagtggaatctggattcctgtctggagtc
 976 to 1050
 GsuI
 BanII
 Eco81I
 Bse21I
 Eco81I
 Bse21I

FIG. 12-7

gatgatgatgcccggtggtggaccctgtgtccgtgagaagcaattgcagcaggaattacttcttatccagcagca
base pairs
ctactactacgggcaccacacctgggacacaggcactcttcgttaacgtcgtccttaataatgaagaataggtcgtcgt
1051 to 1125

DsaI DrrI MfeI Asp700I
BstDSI MunI XmnI

48/173

FIG. 12-8

AlwNI
 gcaacaaatccagaagcagcttctgatagcagagtttcagaacacagcatgagaacttgacacggcagcaccaggc
 base pairs
 cgttggttaggtcttcgtcgaagactatcgtctcaaaagtctttgtcgtactcttgaaactgtgccgtcgtgggtccg
 1126 to 1200

49/173

BlpI	Eco57I	EcoNI	AlwNI
CelII			
tcagcttcaggagcatatcaaggaaacttctagccataaaacagcaacaagaactcctagaaaaggagcagaaact			
base pairs			
agtcgaagtcctcgtatagttcccttgaagatcgggtattttgtcgttggttcttgaggatctttcctcgtctttga			
1201 to 1275			
Bsp1720I			
Bpu1102I			

FIG. 12-9

BpmI
ggagcagcagaggcaagaacagggaagtagagaggcatcgagagaaacagcagcttcctcctctcagagggcaaaaga
base pairs
cctcgtcgtctccggttcttggtccttcattcctccgtagcgtctcttgctcgacgaaggaggagagtcctccggtttct
1276 to 1350
GsuI
EcoNI
50/173

HindIII
tagaggacgagaaaaggcagtggaagtagacagaagtaaaagcag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccggtcacccgttcattgtcttcatttcgtc ttcgaaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 12-10

Van91I	Van91I	
AccB7I	AccB7I	
aacgaaagacactccaactaatggaaaaaatcattccgtgagccgccatcccaagctctggtacacggctgcccc		
base pairs		
ttgcttttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgcagaccatgtgccgacgggt		
1426 to 1500		
Esp1396I	Esp1396I	51/173
PflMI	PflMI	

ccacacatcattggatcaaagctctccacccttagtggaacatctccatcctacaagtacacattaccaggagc	
base pairs	
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcattgtgtaatgggtcctcg	
1501 to 1575	

FIG. 12-11

52/173

Alw21I	BstBI		
AspHI	Bpu14I	FriOI	
	Csp45I	Eco24I	
acaagatgcaaaggatgattcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaaa			
base pairs			
tggtctacgtttcctactaaaggggaagctttttgacggagactcggggttgaacttccacgccagggtccaattt			
1576 to 1650			
BsiHKAI	SfuI	Bsp119I	BanII
Bbv12I	NspV		
	LspI		
	BseRI	EcoNI	
acagaaaagtggcagagaggagaagcagcccccttactcaggcggaaggatggaaatgtgtcacttcattcaagaa			
base pairs			
tgtctttcaccggtctctcctctctcgtcgggggaatgagtcgcgccttcctacctttacaacagtgaaagtaagtctt			
1651 to 1725			

FIG. 12-12

Van91I	Van91I
AccB7I	AccB7I
BpmI PflMI	
gcgaatgttgaggtagacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaacaatgg	
base pairs	
cgcttacaaactccactgtcttaggagtcagtcacgtcaagaggtccgagaccagggtcaagtggttggttacc	
1726 to 1800	
GsuI	Esp1396I
Esp1396I	PflMI
AlwNI	
	53/173

gccaaactggaagtgttactgaaaatgagacttcggtttgccccctacccctcatgccgagcaaatggtttcaca
base pairs
cggttgaccttcacaatgacttttactctgaagcccaaacgggggatggggagtagcggctcgtttaccaaaagtgt
1801 to 1875

FIG. 12-13

BsaMI
Mva1269I
gcaacgcattcctaattcatgaagattccatgaacctgctaagctttataacctctccttcttggcccaacattac
base pairs
cggtgcgtaagattaagtacttctaagggtacttgacgattcagaaatatggagagggaagaaacggggttgtaatg
1876 to 1950
BsmI RcaI
BspHI

BspMI
XcmI

54/173

ErhI
BssT1I
cttgggggttcccgcagtgccatcccagctcaatgcttcgaattcactcaagagaaaagcagaagtgtagagacgca
base pairs
gaaccccgaaagggcggtcacggtagggcgaggtacgaagcttaagtgagtttcttttcgtcttcacactctgcgt
1951 to 2025
EcoT14I
SfuI Bsp119I
BsmBI
StyI
Eco130I
NspV ApoI
LspI EcoRI

FIG. 12-14

55/173

MsII
gacgcttaggcaaggtgttcctctgtcctgggcagtagtgaggcagcatcccggcatctccagccaccctcatgt
base pairs
ctgcgaatccgttccacaaggagacgacccggtacacctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

PstI
SfiI
tactttaggggaaagccaccaccaacagcagcaccaggctctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctccctttcgggtgggtgtcgtcgggtgggtccgagag gacgtcgtataataaactttcttgtttacgc
2101 to 2175
BstSFI

FIG. 12-15

56/173

<p>HindIII</p> <p>acagcaaaagcttctttagctgggtggagttcccttacatcctcagtcctcccttggcaacaaagagagaatttc</p> <p>base pairs</p> <p>tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagaggggaaccgttggtttctctcttaaag</p> <p>2176 to 2250</p>	<p>Eco130I</p> <p>StyI</p> <p>EcoT14I</p> <p>ApoI</p>
<p>Asp718I</p> <p>Acc65I</p> <p>BshNI</p> <p>acctggcattagagggtaccacacaaattgccccgtcacagacccctgaaccgaaccagtcctgcacctttgcctca</p> <p>base pairs</p> <p>tggaccgtaatctccatgggtgtttaacggggcagtgctctggggacttggcttgggtcagacgtggaaacggagt</p> <p>2251 to 2325</p>	<p>Bst1I</p> <p>ErhI</p> <p>AcsI</p> <p>BsgI</p>
<p>BanI</p> <p>KpnI</p> <p>AccB1I</p> <p>Eco64I</p>	

FIG. 12-16

57/173

Bpu1102I
 Alw21I Bsp1720I
 AspHI CelII
 gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttgagaaagcagaataaccagcagca
 base pairs
 ctcgtagcaaccgagtcgaccagtaagtgtcggtggtcggttaagaacctcttcgtcttcggttatgggtcgtcgt
 2326 to 2400
 BsiHKA I PvuII
 Bbv12I B1pI MspA1I
 NspBII
 MflI
 XhoII
 gatccacatgaacaaactgcttttcgaaatctattgaacaaactgaagcaaccaggcagtcaccttgaggaagcaga
 base pairs
 ctagggtgacttggttgacgaaaagctttagataaacttggtgacttcggttggtccggtcagtggaactccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 SfuI Bsp119I
 NspV
 LspI
 BstBI
 Bpu14I
 Csp45I
 Eco57I

FIG. 12-17

58/173

EarI
 Eam1104I
 Asp700I
 Bbv16II
 BbsI Bsp143II
 ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
 base pairs
 ccttctcgaagtcctccctgggtccgctacgtccttctgtctcgcgggagatcacccgttgctcgtgatccctcgctgtc
 2476 to 2550

XmnI Eco57I
 Ksp632I
 SspI
 BpiI HaeII
 BpuAI BstH2I

BcgI
 cagtgccttggtggatgacacactgggacaagtggggctgtgaagggtcaaggaggaaaccagtggacagtgatga
 base pairs
 gtcacgaaacacacctactgtgtgacctgtgtcaacccccgacacttccagttcctccttggtcacctgtcactact
 2551 to 2625

FIG. 12-18

MflI Van91I
 XhoII AccB7I
 agatgctcagatccaggaaatggaatctggggagcaggctgcttttatgcaacagcctttccttggaacccacgca
 base pairs
 tctacgagtcctaggtcctttaccttagacccctcgccgacgaaatacgttgctcgaaaggaccttgggtgcgt
 2626 to 2700
 BstYI Esp1396I
 BstX2I PflMI

59/173

PmaCI
 PmlI
 AflIII
 NspBII
 Esp3I
 cacacgtgcgctctctgtgcgccaagctccgctggctgcggttggcatggatggattagagaaacacccgtctcgt
 base pairs
 gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctaatactcttggcagagca
 2701 to 2775
 MslI Eco72I
 MspAII
 BsmBI
 BsaAI
 BbrPI

FIG. 12-19

60/173

	EarI		BsrDI	BpmI
	Eam1104I			
ctccaggactcactcttccccctgctgcctctgtttacctcaccagcaatggacggccccctccagcctggctc				
base pairs				
gaggtcctgagtgagaaggggacgacggagacaaaaatggagtgggtcgttacctggcgggggaggtcggaccgag				
2776 to 2850				
GsuI	Ksp632I			GsuI

	XcmI
tgcaactggaattgccttatgaccccttgatgctgaaacaccagtgcggtttgtggcaattccaccaccacctga	
base pairs	
acgttgaccttaacggatactggggaaactacgacttttggtcacgcaaacacggttaagggtgggtgggact	
2851 to 2925	

FIG. 12-20

sphI
 BbuI
 gcattgctggacgaatacacagagtatctggtcacgactgcaagaaactgggctgctaataaatgtgagc gaattca
 base pairs
 cgtagacactgcttatgtctcatagaccagtgtgacgttctttgacccgacgattttattacactcg cttaaagt
 2926 to 3000
 PaeI
 NspI
 AcsI
 ApoI
 EcoRI

61/173

AggTCGAAAAGCCAGCCTGGAGGAAATACAGCTTGTTcattctgaacatcactcactgttgtagtggcaccacccc
base pairs
tccagcttttcggtcggaacctcctttatgtcgaacaaagtaagactttagtgagtgacaacataccgtggttggg
3001 to 3075

BpmI
AccB1I
BshNI
BanI
Eco64I
GsuI

FIG. 12-21

62/173

ErhI
StyI Eco130I
EcoT14I
BstXI AlwNI
cctggacggacagaagctggaccccaggataactcctaggtgatgactctcaaaagttttttccctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaggagtaatggaac
3076 to 3150

BstT1I
AvrII
BlnI

BsaWI BsgI
tggtggacttggggtggacagtgacaccatttgggaatgagctacactcgctccggtgctgcacgcatgggctgttg
base pairs
accacctgaacccacacctgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
3151 to 3225

FIG. 12-22

CvnI CfrI
AocI DraII EaeI
Bsu36I Eco57I
ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggtttgtgtgtgtgagggcccttgg
base pairs
gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttaccacaaacgacaacactccgggggacc
3226 to 3300
Eco81I EcoO109I
Bse21I

63/173

MscI ErhI Ecol30I
BstXI BstXI
Eco57I MslI DsaI
ccatcacgctgaagaatccacagccatgggttctgtcttttaattcagttgcaattaccgccaatacttgag
base pairs
ggtagtgcgacttcttaggtgtcgggtaccccaagacgaaaaaattaaagtcaacgttaatggcggttatgaactc
3301 to 3375
MluNI
Bali
EcoT14I
StyI BstDSI
NcoI Bsp19I

FIG. 12-23

BstX2I	NcoI Bsp19I Asp718I	SseBI
BstYI	StyI BstDSI AccB1I	
	Eco147I	
BsaI	XhoII EcoT14I BshNI	StuI
	agaccaaataataagcaagataattgattgttagatctggatgttcaccatggaaacgggtaccagcagcctt	
	base pairs	
	tctggttgatttatattcgttctataactaacatctagacctacaagtggtagccttggccatgggtcggtccggaa	
3376 to 3450		
Eco31I	BglII Bst1I Bani KpnI	AatI
	MflI	ErhI Eco130I Eco64I
		DsaI Acc65I
		Pme55I

SspBI
Bsp1407I
MslI
Asp700I

ttatgctgacccagcatcctgtacatttcactccatcgctatgatgaagggaacttttccctggcagtggagc
base pairs
aatagactgggggcgttaggacatgtaaagtgaggtagcgatactacttcccttgaaaaaggaccgtcacctcg
3451 to 3525

BsrGI
XmnI

FIG. 12-24

<p> FriOI Eco24I cccaaatgaggttggaacaggccttgagagagggtacaataataattgcctggacaggtggccttgatcctcc base pairs gggtttactccaaccttgctcgggaacctcttcccatgttatattataaaggacctgtccaccggaactaggagg 3526 to 3600 BanII AatI StyI Pme55I Eco130I EcoT14I </p>	<p> SseBI ErhI Eco147I StuI BssT1I SspI </p>	<p> 65/173 NcoI Bsp19I StyI BstDSI EcoT14I catgggatgttgagtaccttgaagcattcaggaccatcgtgaagcctgtggccaaagagtttgatccagacat base pairs gtacctctacaactcatggaacttcgtaagtcctggtagcacttcggacacccgggttctcaaaactaggtctgta 3601 to 3675 BssT1I DsaI ErhI Eco130I </p>	<p> MscI MluNI EaeI Mva1269I BsaMI BsmI CfrI BalI Tth111I AtsI AspI </p>
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FIG. 12-25

66/173

MunI

FIG. 12-26

Mph1103I
 EcoT22I
 Ppu10I
 BpmI
 tgatctcacagccatctgtgatgcatacagaagcctgtgtgtaaatgcccttctaggaaatgagctggagccacttgc
 base pairs
 actagagtgtcggtagacactacgtagtcttcggacacatttacgggaagatcccttactcgacctcgggtgaacg
 3826 to 3900
 NsiI
 Zsp2I
 GsuI
 67/173
 Asp700I
 BsaMI
 Mva1269I
 ApeI
 agaagatatctccaccacaaagccgaatatgaatgctgttattctttacagaagatcattgaaattcaaagtat
 base pairs
 tcttctataagaggtggttcgggcttatacttacgacaataaagaaatgtcttctagtaactttaagttcata
 3901 to 3975
 XmnI
 BsmI
 AclI

FIG. 12-27

MflI	AccB1I	AvaI	BcoI
BstI	BsaWI	MflI	Eco88I
BamHI	BshNI	XhoII	Cfr9I
		SmaI	MslI
gtctttaaagtctctggatccggtaccagattacaaggacgacgatgacaagtagat cccgggtggcatccctg			
base pairs			
cagaaatttcaagagacctaggccatgggtctaattgttcctgctgctactgttcatccta gggcccaccgtagggac			
3976 to 4050			
XhoII	BanI	BstYI	Ama87I
BstYI	Acc65I	BstX2I	BsoBI
BstX2I	Asp718I	XmaI	PspAI
68/173			
EcoI30I		GsuI	
StyI		MslI	
EcoT14I			
tgaccctccccagtcctctcctggccttggaagttgccactccagtgcccaccagccttgtcctaataaaatt			
base pairs			
actgggaggggtcacggagagaccggaaccttcaacggtgaggtcacgggtggtcggaacaggattattttaa			
4051 to 4125			
BssT1I		BpmI	
ErhI			

FIG. 12-28

BcoI
 Ama87I
 BcgI
 AvaI
 tggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctcagcctcccgagttgttgggattccag
 base pairs
 accgagtgcggttagagggcgaggaccaccaagtctcgtaagaggacggagtcggagggctcaacaaccctaaggctc
 4276 to 4350

Eco88I
 BsoBI

70/173

NspI
 PaeI Mph1103I
 Ppu10I EcoT22I
 gcattgcattgacccaggctcagctaattttgtttttgttagagacgggtttcaccataattggccaggctggtc
 base pairs
 cgtacgtactgggtccgagtcgattaaaaaaccatctctgtcccccaaaagtgtataaccgggtccgaccag
 4351 to 4425
 BbuI Zsp2I CelII
 SphI Bsp1720I
 NsiI Bpu1102I
 BsmBI
 CfrI
 BalI
 MscI
 MluNI
 EaeI

FIG. 12-30

71/173

BsaI Eco130I
StyI
EcoT14I BstXI
tccaaactcctaattcaggatctaccacaccttggcctcccaattgctgggattacaggcgtgaaccactgct
base pairs
aggttgaggattagagtcactagatgggtggaaccggagggtttaacgacccctaattgtccgcacttgggtgacga
4426 to 4500
Eco31I BstT1I
ErhI

FIG. 12-31

BblII NcoI
 HinII StyI
 AclI AatII EcoT14I
 DraI
 cccttcctgtccttctgtattttaaataactataccagcaggagcgtccagacacagcataggctacctgcc
 base pairs
 gggaaggacaggaagactaaaattttattgatatggtcgctcctcctgcagggtctgtgtcgtatccgatggacgg
 4501 to 4575
 Msp17I BstII
 BsaHI ErhI
 Hsp92I BspMI

72/173

Eco130I BsrFI PflMI
 DsaI AgeI Bse118I
 BsaWI AccB7I
 atggcccaaccgggtgggacatttgagttgcttgccactgtcctctcatgctgggtccactcagtagatg
 base pairs
 taccgggttgccaccctgtataactcaacgaaccgtgacaggagtagtaccgaaccaggtagtcatctac
 4576 to 4650
 BssAI Esp1396I
 BstDSI PinaI Van91I
 Bsp19I Cfr10I

FIG. 12-32

EaeI AlwNI
 cctgttgaattgggtacgcggccagcttctgtggaatgtgtgcagttaggggtgtggaagggtccccagggtcccc
 base pairs
 ggacaacttaaccatgcgcgcggtcgaagacacaccttacacacagtcaatcccacaccttcagggtccgagggg
 4651 to 4725
 CfrI

73/173

NspI
 PaeI Mph1103I
 Ppu10I EcoT21I SexAI
 agcaggcagaagtatgcaaaagcatgtcatctcaattagtcagcaaccagggtgtggaaaaagtcctccagggtccccag
 base pairs
 tcgtccgtcttcatacgtttcgtacgttagagttaatcagtcgttggtccacaccttttcagggtccgaggggtc
 4726 to 4800
 BbuI Zsp2I
 SphI
 NsiI

FIG. 12-33

74/173

NspI
PaeI Mph1103I
Ppu10I EcoT22I
caggcagaagtatgcaaagcatgcatctcaattagtcagcaaccatagtcgcgcccctaactccgcccattccccgc
base pairs
gtccgtcttcatacgtttcgtacgtagagttaatcagtcgttggtatcagggcggggattgaggcgggtagggcg
4801 to 4875

BbuI Zsp2I
SphI
NsiI

NcoI Bsp19I
StyI BstDSI
EcoT14I
ccctaactccgcccagttccgcccattctccgcccattggctgactaatTTTTTTTatttatgcagagcccgagg
base pairs
gggattgaggcgggtcaaggcgggtaagagcggggtaccgactgattaaaaaaaaataacgtctccggctcc
4876 to 4950

BstT1I
ErhI Eco130I
DsaI

FIG. 12-34

SseBI AvrII
 Eco147I BlnI
 StuI BstXI
 BglI BseRI
 ccgcctcggcctctgagctattccagaagtagtgaggaggcttttttgaggcctaggcttttgcaaaaagctc c
 base pairs
 ggaggagccggagactcgataaaggcttctcatcactcctccgaaaaaacctccggatccgaaaacggttttttcgagg
 4951 to 5025
 SfiI
 AatI StyI
 Pme55I ErhI
 EcoT14I Eco130I

75/173

Ama87I
 Eco88I BseRI
 AvaI BsoBI
 SfiI Apol
 tcgaggaactgaaaaaccagaaagttaattccctatatagtgagtcgtattaaattcgtaatcatggtcatagctgt
 base pairs
 agctccttgacttttggcttttcaattaagggatatacactcagcataaatttaagcattagtagcagtagtcgaca
 5026 to 5100
 XhoI BcoI
 Sfr274I
 PaeR7I
 BstSFI
 Acsi

FIG. 12-35

76/173

AccBSI
BsrBI
ttcctgtgtgaaattgttatccgctcacattccacacaacatacagagccggaagcataaagtgtaaagcctggg
base pairs
aaggacacactttaacaataggcgagtggttaagggtgtgtgtatgctcggccttcgtatttcacatttcggaccc
5101 to 5175
BstD102I

AccB1I
BshNI
gtgcctaagtgtgagctaaactcacattaatgctgtgctcactgcccgcttccagtcgggaaacctgtcgt
base pairs
cacggattactcactcgattgagtgtaattaacgcaacgcgagtgacgggcgaaaggtcagccctttggacagca
5176 to 5250
Bani
Eco64I
VspI
PshBI
AsnI
AseI

FIG. 12-36

VspI
 MspA1I
 PvuII PshBI EaeI
 gccagctgcattaatgaatcggccaaacgcgcgggagagcggttgcgtattggcgctcttccgcttccctcgc
 base pairs
 cggtcgacgtaattacttagccggttgcgcgccctctccgccaacgcataacccgcgagaaggcgaaggagcg
 5251 to 5325
 NspBII CfrI
 AsnI
 AseI
 BstMCI
 BsaOI
 tcaactgactcgctgcgctcggttcggttcggtcgccgagcggtatcagctcactcaaaggcggtaatacggttat
 base pairs
 agtgactgagcgacgcgagccagcaagccgacgcgctcgccatagtcgagtgagtttccgcccattatgcccaata
 5326 to 5400
 Bsh1285I
 BsiEI
 BstD102I
 BstH2I
 Bsp143II
 HaeII EarI
 Sapi
 Ksp632I
 AccBSI
 BsrBI
 77/173

77/173

FIG. 12-37

78/173

NspI

BspLU11I

ccacagaatcaggggataaacgcaggaagaacatgtgagcaaaaggccagcaaaaggccaggaaccgtaaaaaagg
base pairs
ggtgtcttagtccccctattgcgtcctttcttgtaactcgttttccggtcgttttccggtccttggcatttttcc
5401 to 5475

AflIII

DrdI

ccgcgttgctggcgtttttccataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcaagaggt
base pairs
ggcgcaacgacccgcaaaaaaggatccgaggcggggggactgctcgtagtggttttagctgcgagttcagtcctcca
5476 to 5550

FIG. 12-38

		BsiI		
ggcgaaacccgacaggactataaagataccaggcggtttccccctggaagctccctcgtagcgctctcctgttccga				
base pairs				
ccgctttgggctgtcctgatatttctatggtccgcaaaaggggaccttcgagggagcacgcgagaggacaaggct				
5551 to 5625				
		BssSI		
79/173				
	BsaWI	BstH2I	Bsp143II	SfiI
ccctgccgcttacccggatacctgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgta				
base pairs				
gggacggcggaatggcctatggacagggcggaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacat				
5626 to 5700		HaeII		BstSFI

FIG. 12-39

BsiHKAI
 NspBII
 BstMCI
 BsaOI
 Alw44I
 VneI Bbv12I
 ggtatctcagttcgggtgtaggtcggtccaaagctgggtgtgtgtgcacgaaccccccggttcagccccgaccgct
 base pairs
 ccataaggtcaagccacatccagcaagcgaggttcgacccgacacacgtgcttggggggaagtcgggctggcgga
 5701 to 5775

ApaLI
 Bsh1285I
 AspHI
 BsiEI
 Alw21I
 MspAII
 80/173

BsaWI
 AlwNI
 ggccttatccggtaactatcgtcttgagtcacacccggtaagacacgacttatcgccactggcagcagccactg
 base pairs
 cgcggaataggccattgatagcagaactcaggttggggccattctgtgtgctgaatagcggtgaccgtcggtcggtgac
 5776 to 5850

FIG. 12-40

81/173

SfclI

gtaacaggattagcagagcgaggatgtaggcgggtgctacagagttcttgaagtggcctaactacgggtaca
base pairs
cattgtccctaatacgtctcgctccatacatccgccacgatgtctcaagaacttcaccaccggattgatgccgatgt
5851 to 5925

BstSFI

Eco57I

ctagaagaacagtatttgggtatctgcgctctgctgaagccaggttaccttcggaaaaagagtggtagctcttgat
base pairs
gatcttcttgatcataaaaccatagacgcgagacgacttcggtcaatggagccctttttctcaaccatcgagaacta
5926 to 6000

FIG. 12-41

MflI
 XhoII
 NspBII
 ccggcaaaaccaccgctggtagcgggtgtttttgttgcaagcagcagattacgcgcagaaaaaaggat
 base pairs
 ggccgtttgttggtggcgaccatcgccacaaaaaacgctcgtcctaatacgcggtccttttttttccta
 6001 to 6075
 MspAII
 BstYI
 BstX2I

82/173

MflI
 XhoII
 ctcaagaagatccttttgatcttttctacgggtctgacgctcagtggaacgaaaaactcacgtaaggatttgg
 base pairs
 gagttcttctaggaactagaaaagatgcccagactgcgagtcaccttgcttttgagtgaattccctaaacc
 6076 to 6150
 BstYI
 BstX2I

FIG. 12-42

83/173

RcaI	MflI	MflI	DraI
	XhoII	XhoII	
tcatagagattatcaaaaaggatccttcacctagatccttttaaatataaaatgaagtttttaaatcaatctaaagta			
base pairs			
agtactctaatagtttttcctagaagtggtggtcctaggaataatttaattttacttcaaaatttagttagatttcacat			
6151 to 6225			
BspHI	BstYI	BstYI	
	BstX2I	BstX2I	

	AccB1I
	BshNI
tatatgagtaaaacttggtctgacagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttc	
base pairs	
atatactcatttgaaccagactgtcaatgggttacgaattagtcactccgtggatagatcgctagacagataaag	
6226 to 6300	
	BanI
	Eco64I

FIG. 12-43

84/173

Eam1105I
 AspEI
 gttcatccatagttgcctgactccccgctcgtgtagataactacgatacgggagggttaccatctggccccagtg
 base pairs
 caagtaggtatcaacggactgaggggcagcacatctattgatgctatgccctcccgaatggtagaccgggtcac
 6301 to 6375
 EclHKE
 AhdI

Cfr10I
 BsrDI BsaI BssAI BpmI BglI
 ctgcaatgataccgcgagaccacgctcaccggctccagatttatcagcaataaaccagccagccggaaggccg
 base pairs
 gacgttactatggcgctctgggtgcgagtgccgaggtctaaatagtcgttatttggtcggtcggccttccccggc
 6376 to 6450
 Eco31I BsrFI GsuI
 Bse118I

FIG. 12-44

VspI
PshBI
agcgagaagtggctcctgcaactttatccgcctccatccagtcctatttggtgcccgggaagctagagtaagta
base pairs
tcgcgtcttcaccaggacgttgaatataggcgaggtaggtcagataattaacaacggcccttcgatctcatcat
6451 to 6525

AsnI
AseI

85/173

AviII
FspI
gttcgccagttaatagtttgcgcaacggtgttgccattgctacaggcatcgtggtgtcacgctcgtcgtttggta
base pairs
caagcgggtcaattatcaaacgcgttgcaacaacggtaacgatgcgtagcaccacagtcgcgagcagcaaacat
6526 to 6600
Acc16I
BsrDI
Psp1406I

FIG. 12-45

BsaWI
 tggcttcattcagctccggttcccaacgatcaaggcgaggttacatgatcccccatgttgtgcaaaaaagcgggta
 base pairs
 accgaagtaagtcgaggccaagggttgctagtccgctcaatgtactaggggtacaaacacggttttttcgccaat
 6601 to 6675

86/173

BstMCI
 PvuI BsiEI
 BsaOI EaeI MslI
 gctccttcggtcctccgatcgttgtcagaagtaagttggccgcagtggttatcactcatgggttatggcagcactgc
 base pairs
 cgaggaagccaggaggtagcaacagtccttcattcaaccggcggtcacaatagtgtgagtaaccaataccgtcgtgacg
 6676 to 6750
 BspCI CfrI
 Bsh1285I
 Ple19I

FIG. 12-46

Acc113I
 Eco255I
 ataattcttactgtcatgccatccgtaagatgcttttctgtgactggtagtactcaaccaagtcattctgag
 base pairs
 tattaagagaatgacagtagcgtaggcattctacgaaaagacactgaccactcatgagttggttcagtaagactc
 6751 to 6825
 ScaI

87/173

BbiII
 BstMCI
 BsaOI
 BcgI
 Bsh1285I
 BsiEI
 Bsp17I
 BsaHI
 Hsp92I
 aatagtgtatgcggcgaccgagttgctcttgcggcggtcaatacgggataataccgcccacatagcagaactt
 base pairs
 ttatcacatacgccgctggctcaacgagaacggcgccgagttatgccctattatggcgcggtgtatcgtcttgaa
 6826 to 6900

FIG. 12-47

88/173

Alw21I	XmnI	MflI	MflI
AspHI	Psp1406I	XhoII	NspBII XhoII
taaaagtgcctcatcattggaaaaacgttcttctggggcgaaaaactctcaaggatcttaccgctgttgagatccagtt			
base pairs			
attttcacgagtagtaaccttttgcaagaagccccgcgttttgagagttcctagaatggcgacaactctagggtcaa			
6901 to 6975			
BsiHKAI	Asp700I	BstYI	MspAII BstYI
Bbv12I		BstX2I	BstX2I

BssSI	Eco57I
Alw44I Bbv12I	
VneI BsiHKAI	
cgatgtaaccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaa	
base pairs	
gctacattgggtgagcacgtgggtgactagaagtcgtagaaaatgaaagtgggtcgcaagaccactcgttttt	
6976 to 7050	
ApalI Alw21I	
BsiI	
AspHI	

FIG. 12-48

EarI
 MslI
 Ham1104I
 caggaaggcaaaatgccgcaaaaaagggaataaagggcgacacggaatgttgaatactcactcttccttttc
 base pairs
 gtccttcggttttacggcggtttttcccttattcccgctgtgcctttacaacttatgagtatgagaaggaaaaag
 7051 to 7125
 Ksp632I

89/173

SspI
 RcaI
 AccBSI
 BsrBI
 aatattattgaagcatttatcagggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaac
 base pairs
 ttataataacttcgtaaatagtcaccaataaacagagtagtgcctatgtataaaacttacataaatctttttatttg
 7126 to 7200
 BspHI
 BstD102I

FIG. 12-49

SfcI
 aaataggggttcgcgcacatttccccgaaaagtgcacacctgacgcgccctgtagggcgcatataagcgcggcgg
 base pairs
 ttatatccccaaggcgcgtgtaaaaggggcttttcacgggtggactgcgcgggacatcgccgcgtaattcgcgcgcgcc
 7201 to 7275

BstSFI

90/173

AccBSI
 BstH2I HaeII BstD102I
 Bsp143II BsrBI
 gtgtggtggttacgcgcagcgtgaccgctacacttgccagcgccttagcgcgccctccttctcgctttcttccctt
 base pairs
 cacaccaccaatgcgcgtcgcactggcgatgtgaacggtcgcgggatcgcgggcgaggaagcgaagaaagggaa
 7276 to 7350

HaeII Bsp143II
 BstH2I

FIG. 12-50

91/173

BsrFI
 BsaAI NaeI
 MroNI Bse118I
 cctttctgccacgttcgccggctttcccggtcaagctctaaatcggggcatcccttttagggtccgatttagtg
 base pairs
 ggaaagagcgggtgcaagcggccgaaaggggcagttcgagatttagccccgtaggggaaatcccaaggctaataacac
 7351 to 7425

NgoAIV
 NgoMI
 Cfr10I

AccB1I
 BshNI
 BsaAI
 ctttacggcacctcgacccccaaaaacttgattagggatggttcacgtagtgggccatcgccctgatagacgg
 base pairs
 gaaatgccgtggagctgggggtttttgaactaatcccactaccacgaagtgcacccggtagcgggactatctgcc
 7426 to 7500
 Bani
 Eco64I
 DraIII

FIG. 12-51

92/173

DrdI

tttttcgcccttgacgttgaggtccacgttctttaatagtggaactctgttccaaactgggaacaacactcaacc
base pairs
aaaaagcgggaaactgcaacctcaggtgcaagaaattatcacctgagaacaaggtttgacctgtgtgagttgg
7501 to 7575

ctatctcgggtctattctttgatattataagggatttttgccgatttcggcctattgggttaaaaaatgagctgattt
base pairs
gatagagccagataagaaaaactaaatattccctaaaacgggctaagccggataaccaattttttactcgactaaa
7576 to 7650

FIG. 12-52

ApoI ApoI SspI Psp1406I
 aacaaaaatttaacgcgaattttaacaaaaataataacggtttacaattt base pairs
 ttgtttttaaatgcttaaaattgttttataatttgcaaatgttaaa 7651 to 7699
 ACSI ACSI

Table by Enzyme Name

Enzyme name	No. cuts of sites	Positions	Recognition sequence	
AatI	3	3446 3546 5002	agg/cct	<u>More info</u>
AatII	5	451 504 587 773 4550	gacgt/c	<u>More info</u>
Acc113I	1	6804	agt/act	<u>More info</u>
Acc16I	2	21 6546	tgc/gca	<u>More info</u>
Acc65I	3	2264 3434 3998	g/ gtacc	<u>More info</u>
AccB1I	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	<u>More info</u>
AccB7I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	<u>More info</u>
AccBSI	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
Ac1NI	1	326	a/ ctagt	<u>More info</u>
AcSI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	<u>More info</u>
AcYI	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>

FIG. 12-53

AflIII	3	2702 3796 5431	a/ crygt	<u>More info</u>
AgeI	1	4584	a/ ccggt	<u>More info</u>
AhdI	2	4150 6324	gacnnn/nngtc	<u>More info</u>
Alw21I	6	894 1576 2330 5749 6910 6995	gwgw/c	<u>More info</u>
Alw44I	2	5745 6991	g/ tgcac	<u>More info</u>
AlwNI	6	1147 1273 1775 3091 4678 5847	cagnnn/ctg	<u>More info</u>
Ama87I	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
AocI	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
ApaI	1	4202	gggcc/c	<u>More info</u>
ApalI	2	5745 6991	g/ tgcac	<u>More info</u>
ApoI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	<u>More info</u>
AseI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
AsnI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
Asp700I	5	1107 2481 3506 3906 6923	gaann/nnttc	<u>More info</u>
Asp718I	3	2264 3434 3998	g/ gtacc	<u>More info</u>

FIG. 12-54

95/173

FIG. 12-55

BclI	1	969	t/ gatca	<u>More info</u>
BcoI	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
BglI	5	14 417 538 4956 6444	gccnnnn/nggc	<u>More info</u>
BglII	2	932 3409	a/ gatct	<u>More info</u>
BlnI	2	3109 5003	c/ ctagg	<u>More info</u>
BlpI	3	1200 2337 4366	gc/tnagc	<u>More info</u>
BpiI	2	2512 4216	gaagac	<u>More info</u>
BpmI	10	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
		3892 4097 4259 6414		
Bpu1102I	3	1200 2337 4366	gc/tnagc	<u>More info</u>
Bpu14I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BpuAI	2	2512 4216	gaagac	<u>More info</u>
Bsa29I	1	939	at/ cgat	<u>More info</u>
BsaAI	3	666 2705 7473	yac/gtr	<u>More info</u>
BsaHI	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>
BsaI	3	3380 4427 6396	ggtctc	<u>More info</u>
BsaMI	3	1886 3631 3936	gaatgc	<u>More info</u>
BsaOI	7	42 424 928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BsaWI	6	3200 3995 4584 5637 5784 6615	w/ ccggw	<u>More info</u>
BscI	1	939	at/ cgat	<u>More info</u>

96/173

FIG. 12-56

97/173

Bse118I	3	4584	6404	7368	r/ ccggy	<u>More info</u>
Bse211I	3	1034	1046	3256	cc/ tnagg	<u>More info</u>
BseCI	1	939			at/ cgat	<u>More info</u>
BseRI	5	1337	1671	3725 4989 5027	gaggag	<u>More info</u>
BsgI	3	2315	3212	4264	gtgcag	<u>More info</u>
Bsh1285I	7	42 424 928 5347 5771 6694 6843			cgry/cg	<u>More info</u>
BshNI	8	791 2264 3065 3434 3998 5175			g/ gyrcc	<u>More info</u>
		6272 7432				
BsiEI	7	42 424 928 5347 5771 6694 6843			cgry/cg	<u>More info</u>
BsiHKAI	6	894 1576 2330 5749 6910 6995			gwgcw/c	<u>More info</u>
BsiI	2	5609 6993			ctcgtg	<u>More info</u>
BsmBI	3	2023 2773 4397			cgtctc	<u>More info</u>
BsmI	3	1886 3631 3936			gaatgc	<u>More info</u>
BsoBI	3	4034 4330 5025			c/ ycgrrg	<u>More info</u>
Bsp106I	1	939			at/ cgat	<u>More info</u>
Bsp119I	3	1603 1988 2423			tt/cgaa	<u>More info</u>
Bsp120I	1	4198			g/ ggccc	<u>More info</u>
Bsp1407I	2	270 3471			t/ gtaca	<u>More info</u>
Bsp143II	5	2519 5309 5679 7318 7326			rgcgc/y	<u>More info</u>
Bsp1720I	3	1200 2337 4366			gc/tnagc	<u>More info</u>
Bsp19I	6	686 3324 3424 3600 4574 4910			c/ catgg	<u>More info</u>

FIG. 12-57

98/173

BspCI	2	42 6694	cgat/cg	<u>More info</u>
BspDI	1	939	at/ cgat	<u>More info</u>
BspHI	3	1891 6151 7159	t/ catga	<u>More info</u>
BspLU11I	1	5431	a/ catgt	<u>More info</u>
BspMI	2	1913 4574	acctgc	<u>More info</u>
BspXI	1	939	at/ cgat	<u>More info</u>
BsrBI	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BsrDI	4	245 2827 6383 6565	gcaatg	<u>More info</u>
BsrFI	3	4584 6404 7368	r/ ccggy	<u>More info</u>
BsrGI	2	270 3471	t/ gtaca	<u>More info</u>
BssAI	3	4584 6404 7368	r/ ccggy	<u>More info</u>
BssSI	2	5609 6993	ctcgtg	<u>More info</u>
BssT1I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	<u>More info</u>
BstBI	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BstD102I	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BstDSI	7	686 1062 3324 3424 3600 4574 4910	c/ crygg	<u>More info</u>
Bsth2I	5	2519 5309 5679 7318 7326	rgcgc/y	<u>More info</u>

FIG. 12-58

BstI	1	3992		g/ gatcc	<u>More info</u>
BstMCI	7	42 424 928 5347 5771 6694 6843		cgry/cg	<u>More info</u>
BstSFI	8	944 2144 4220 5058 5696 5887		c/ tryag	<u>More info</u>
		6565 7250			
BstSNI	1	666		tac/gta	<u>More info</u>
BstX2I	12	932 2400 2634 3409 3992 4030		r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966			
BstXI	3	3076 3325 4473		ccannnn/ntgg	<u>More info</u>
BstYI	12	932 2400 2634 3409 3992 4030		r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966			
BstZI	1	925		c/ ggccg	<u>More info</u>
Bsu15I	1	939		at/ cgat	<u>More info</u>
Bsu36I	3	1034 1046 3256		cc/ tnagg	<u>More info</u>
CciNI	1	925		gc/ggccgc	<u>More info</u>
CelII	3	1200 2337 4366		gc/tnagc	<u>More info</u>
Cfr10I	3	4584 6404 7368		r/ ccggy	<u>More info</u>
Cfr9I	1	4034		c/ ccggg	<u>More info</u>
CfrI	10	152 182 236 925 3298 3651 4412		y/ ggccr	<u>More info</u>
		4669 5270 6712			
ClaiI	1	939		at/ cgat	<u>More info</u>
Csp45I	3	1603 1988 2423		tt/cgaa	<u>More info</u>
CvnI	3	1034 1046 3256		cc/ tnagg	<u>More info</u>

99/173

FIG. 12-59

DraI	5	3981	4523	6190	6209	6901	ttt/aaa	<u>More info</u>
DraII	3	3291	4198	4225			rg/gnccy	<u>More info</u>
DraIII	1	7476					cacnnn/gtg	<u>More info</u>
DrdI	3	1076	5539	7520			gacnnnn/nngtc	<u>More info</u>
DsaI	7	686	1062	3324	3424	3600 4574	c/ cry9g	<u>More info</u>
		4910						
EaeI	10	152	182	236	925	3298 3651 4412	y/ ggccr	<u>More info</u>
		4669	5270	6712				<u>More info</u>
EagI	1	925					c/ ggccg	<u>More info</u>
Eam1104I	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Eam1105I	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EarI	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Ecl1136II	1	892					gag/ ctc	<u>More info</u>
EclHKI	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EclXI	1	925					c/ ggccg	<u>More info</u>
Eco105I	1	666					tac/gta	<u>More info</u>
Eco130I	13	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574 4910		
		5003						
Eco147I	3	3446	3546	5002			agg/cct	<u>More info</u>

100/173

FIG. 12-60

101/173

Eco24I	5	894	1017	1623	3526	4202	grgcy/c	<u>More info</u>
Eco255I	1	6804					agt/act	<u>More info</u>
Eco31I	3	3380	4427	6396			ggtctc	<u>More info</u>
Eco32I	1	952					gat/atc	<u>More info</u>
Eco52I	1	925					c/ggccg	<u>More info</u>
Eco57I	7	1210	2446	2488	3271	3314 5963	ctgaag	<u>More info</u>
		7011						
Eco64I	8	791	2264	3065	3434	3998 5175	g/gyrcc	<u>More info</u>
		6272	7432					
Eco72I	1	2705					cac/gtg	<u>More info</u>
Eco81I	3	1034	1046	3256			cc/tnagg	<u>More info</u>
Eco88I	3	4034	4330	5025			c/ycgrg	<u>More info</u>
EcoICRI	1	892					gag/ctc	<u>More info</u>
EcoNI	4	1259	1338	1684	3723		cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291	4198	4225			rg/gnccy	<u>More info</u>
EcoRI	3	912	1990	2994			g/aattc	<u>More info</u>
EcoRV	1	952					gat/atc	<u>More info</u>
EcoT14I	13	686	1950	2226	3109	3324 3424	c/cwagg	<u>More info</u>
		3547	3600	4077	4456	4574 4910		
		5003						
EcoT22I	5	3703	3850	4357	4752	4825	atgca/t	<u>More info</u>

FIG. 12-61

ErhI	13	686	1950	2226	3109	3324	3424	c/ cwwgg	More info
		3547	3600	4077	4456	4574	4910		
		5003							
Esp1396I	6	1445	1482	1775	1796	2644	4587	ccannnn/ntgg	More info
Esp3I	3	2023	2773	4397				cgtctc	More info
FauNDI	1	560						ca/ tatg	More info
FbaI	1	969						t/ gatca	More info
FriOI	5	894	1017	1623	3526	4202		grgcy/c	More info
FspI	2	21	6546					tgc/gca	More info
GsuI	10	1015	1279	1772	2781	2842	3022	ctggag	More info
		3892	4097	4259	6414				
HaeII	5	2519	5309	5679	7318	7326		rgcgc/y	More info
HinII	6	448	501	584	770	4547	6861	gr/cgyc	More info
HincII	3	311	446	842				gty/rac	More info
HindII	3	311	446	842				gty/rac	More info
HindIII	3	918	1394	2183				a/ agctt	More info
Hsp92I	6	448	501	584	770	4547	6861	gr/cgyc	More info
KpnI	3	2268	3438	4002				ggtac/c	More info
Ksp22I	1	969						t/ gatca	More info
Ksp632I	5	58	2482	2793	5314	7118		ctcttc	More info
LspI	3	1603	1988	2423				tt/cgaa	More info
MfeI	2	1091	3773					c/ aattg	More info
MflI	12	932	2400	2634	3409	3992	4030	r/gatcy	More info

102/173

FIG. 12-62

104/173

PfIMI	6	1445	1482	1775	1796	2644	4587	ccannnn/ntgg	More info
PinAI	1	4584						a/ ccggt	More info
Ple19I	2	42	6694					cgat/cg	More info
PmaCI	1	2705						cac/gtg	More info
Pme55I	3	3446	3546	5002				agg/cct	More info
PmlI	1	2705						cac/gtg	More info
Ppu10I	5	3699	3846	4353	4748	4821		a/ tgcat	More info
PshBI	4	334	5202	5261	6496			at/ taat	More info
Psp124BI	1	894						gagct/c	More info
Psp1406I	3	6550	6923	7687				aa/cggt	More info
PspAI	1	4034						c/ccggg	More info
PspALI	1	4036						ccc/ggg	More info
PspOMI	1	4198						g/ggccc	More info
PstI	2	948	2148					ctgca/g	More info
PvuI	2	42	6694					cgat/cg	More info
PvuII	3	71	2341	5255				cag/ctg	More info
RcaI	3	1891	6151	7159				t/catga	More info
SacI	1	894						gagct/c	More info
SapI	2	2483	5314					gctcttc	More info
ScaI	1	6804						agt/act	More info
SexAI	1	4769						a/ ccwggg	More info
SfCI	8	944	2144	4220	5058	5696	5887	c/ tryag	More info

FIG. 12-64

SfiI	1	6565	7250	ggccnnnn/nggcc	<u>More info</u>
Sfr274I	1	4956		c/ tgcag	<u>More info</u>
SfuI	3	5025		tt/cgaa	<u>More info</u>
SmaI	1	1603	1988 2423	ccc/ggg	<u>More info</u>
SnaBI	1	4036		tac/gta	<u>More info</u>
SpeI	1	666		a/ ctagt	<u>More info</u>
SphI	4	326		gcatg/c	<u>More info</u>
SseBI	3	2930	4355 4750 4823	agg/cct	<u>More info</u>
SspBI	2	3446	3546 5002	t/ gtaca	<u>More info</u>
SSPI	6	270	3471	aat/att	<u>More info</u>
SstI	1	179	226 3571 4164 7128 7681	gagct/c	<u>More info</u>
StuI	3	894		agg/cct	<u>More info</u>
StyI	13	3446	3546 5002	c/ cwwgg	<u>More info</u>
		686	1950 2226 3109 3324 3424		
		3547	3600 4077 4456 4574 4910		
		5003			
Tth111I	1	3674		gacn/nngtc	<u>More info</u>
Van91I	6	1445	1482 1775 1796 2644 4587	ccannnn/ntgg	<u>More info</u>
VneI	2	5745	6991	g/ tgcac	<u>More info</u>
VspI	4	334	5202 5261 6496	at/ taat	<u>More info</u>
XbaI	1	3811		t/ ctaga	<u>More info</u>
XcmI	2	1948	2897	ccannnnn/nnntgg	<u>More info</u>

105/173

FIG. 12-65

XhoI	1	5025				c/ tcgag	<u>More info</u>
XhoII	12	932 2400 2634 3409 3992 4030				r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966					
XmaI	1	4034				c/ ccggg	<u>More info</u>
XmaIII	1	925				c/ ggccg	<u>More info</u>
XmnI	5	1107 2481 3506 3906 6923				gaann/nnttc	<u>More info</u>
Zsp2I	5	3703 3850 4357 4752 4825				atgca/t	<u>More info</u>

106/173

The following endonucleases were selected but don't cut this sequence:

AccI, AccIII, AfeI, AflII, Aor51HI, AscI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, EcoO65I, EheI, FseI, HpaI, Kasi, Kpn2I, KspI, MamI, MluI, MroI, MspCI, NarI, NheI, NruI, PacI, Pfl23II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, SalI, SbfI, Sfr303I, Sgfi, SgrAI, SmiI, SphI, SrfI, Sse8387I, SstII, SunI, SwaI, Vha464I

FIG. 12-66

FIG. 13A
FIG. 13B
FIG. 13C
FIG. 13D
FIG. 13E

cccatcgccattcaggctgcgcaactgttgggaaggcgatcgggtcgggacctcttcgtattacgccagctggcgaaaggcg
ggatgtgctgcaaggcgattaagttgggtaacgcccagggtttccagtcacgacgttgtaaaacgacggccagtgccaagct
gatctaatacaataattggccattagccatattattcattggttatatagcataaaatcaataattggctattggccattgcatacgttgatcca
tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgatttactagtagttattaatagtaataattacg
gggtcattagtticatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggcgaccgccagcgaccc
ccgcccgttgacgtcaatagtgacgtatgttcccatagtaacccaataggggactttccattgacgtcaatgggtggagtatttacg
gtaaactgcccacttggcagtagacatcaagtgtagtataatgccaaagtcgccccctattgacgtcaatgacggtaaatggccccgcct
agcattatgccagtagacatgaccttacggggagtttctacttggcagtagacatctacgtattagtcatacgtctattaccatgggtatgcg
gttttgcagtagacccaatggcggtgtagacgggttgactcacggggatttccaaagtcctccacccattgacgtcaatggggaggtt
tgtttggcaccaaaatcaacgggactttccaaaatgtcgtataacccccgcccgttgacgcaaatggcggtagcggtgtacg
gtgggagggtctatataagcagagctcgttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcagagatatac
(EcoRV)
acc

107/173

FIG. 13

FIG. 13A

108/173

ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAGTTCCTGTGGGCTGGAGCCCATCTCACCTTTA
GACCTAAGGACAGACCTCAGGATGATGATGCCCGTGGTGACCCCTGTGTCCGTGAGAAAGCAATTGCAGCAG
GAATTACTTCTTATCCAGCAGCAGCAACAATCCAGAAGCAGCTTCTGTATAGCAGAGTTTCAGAAACAGCAT
GAGAACTTGACACGCGCAGCACCCAGGCTCAGCTCAGGAGCATATCAAGGAACCTTAGCCATAAAACAGCAA
CAAGAACTCCTAGAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAACAGGAAGTAGAGAGGCATCGCAGA
GAACAGCAGCTTCCTCCTCTCAGAGGCAAAAGATAGAGGACGAGAAAGGCGAGTGGCAAGTACAGAAGTAAAG
CAGAAGCTTCAAGAGTTCCTACTAGTAAATCAGCAACGAAAGACACTCCAACCTAATGGAAAATCATTC
GTGAGCCGCATCCCAAGCTCTGGTACACGGCTGCCACACACATCATTTGGATCAAAGCTCTCCACCCCTT
AGTGGAAACATCTCCATCCTACAAGTACACATTAACAGGAGCACAAAGATGCAAAGGATGATTTCCCCCTTCGA
AAAACCTGCCCTCTGAGCCCAACTTGAAGTGCGTCCAGGTTAAACAGAAAGTGGCAGAGAGAGAAAGCAGC
CCCTTACTCAGGCGGAAGGATGGAATGTTGTCACTTCAATTCAGAAGAGCGAATGTTTGAGGTGACAGAAATCC
TCAGTCAGTAGCAGTTCTCCAGGCTCTGGTCCCAGTTCACCAAACAATGGCCCACTGGCAAGTGTACTGAA
AATGAGACTTCGGTTTIGCCCCCTACCCCTCATGCGGAGCAAAATGGTTTCACAGCAACGCAATCTAAATTCAT
GAAGATTCCATGAACCTGCTAAGTCTTTATACCTCTCTCTTTTGCCCCAACATTACCTTGGGGCTTCCCCGCA
GTGCCATCCCAGCTCAATGCTTCGAATTCACCTCAAAGAAAAGCAGAGTGTGAGACGCAGACGCTTAGGCAA
GGTGTTCCTCTGCTGGCAGTATGGAGGCAGCATCCCGCATCTCCAGCCACCCCTCATGTACTTTAGAG
GGAAAGCCACCCAACAGCAGCCACAGGCTCTCCTGCAGCATTTATTTAATGAAAGAACAAATGCCACAGCAA
AAGCTTCTTGTAGCTGGTGGAGTTCCCTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAAATTTACCT
GGCATTAGAGTACCCACAAAATTGCCCGTCAAGACCCCTGAACCGAACCAGTCTGCACCTTTGCCCTCAG
AGCACGTTGGCTCAGTGGTCAATTCACAGCAACACAGCAATTTCTTGGAGAACGAGAAAGCAATACAGCAG
CAGATCCACATGAACAAACTGCTTTCGAAATCTATTGAACAACCTGAAGCAACCCAGGCAGTCACCTTGAGGAA
GCAGAGGAAGAGCTTCAGGGGACCCAGGCGATGCAGGAAGACAGAGCGCCCTCTAGTGGCAACAGCACTAGG
AGCGACAGCAGTGTGTGGATGACACACTGGGACAAGTTGGGGCTGTGAAGGTCAAGGAGGAACCCAGTG
GACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGAGCAGGCTGCTTTTATGCAACAGCCTTTC

FIG. 13B

109/173

CTGGAACCCACGCACACAGTGGCTCTCTGTGCGCCCAAGCTCCGCTGGCTGCGGTTGGCATGGATGGATTAGAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCCTGCTGCCCTCTGTGTTTACCTCACCCAGCAATGGACGCCCCCTCCAGCCTGGCTCTGCAACTGGAATTGCCCTATGACCCCTTGATGCTGAAACACACAGTGCCTTTGTGGCAATTCCACACCCACCTGAGCATGCTGGACGAATAACAGAGTATCTGGTCAAGCTGCAAGAACTGGGCTGCTAAATAAATGTGAGCGAATTCAAGGTCGAAAAGCCAGCCTGGAGGAAATACAGCTTGTTCATTCTGAAATCACTCACTGTGTATGGCACCAACCCCTGGACGGACAGAAGCTGGACCCAGGATACTCCTAGGTGATGACTCTCAAAAGTTTTTTTCTCATTAACCTTGTGGTGGACTTGGGGTGGACAGTGACACCATTTGGAAATGAGCTACACTCGTCCGGTGTGCACGCATGGCTGTGGCTGTGTCTCATCGAGCTGGCTTCCAAAGTGGCCTCAGGAGAGCTGAAGAAATGGGTTTGTGTGAGGCCCTGGCCATCACGCTGAAGAAATCCACAGCCATGGGGTTC TGCTTTTAAATTCAGTTGCAATTACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATTGTAGATCTGGATGTTACCATGGAAACCGTACCAGCAGGCCCTTTTATGCTGACCCAGCATCCTGTACATT TCACTCCATCGCTATGATGAAGGAACTTTTCCCTGGCAGTGGAGCCCCCAAAATGAGGTTTCGGTTTATTCTCTTAGAGCCCCCACTTTTATTTTGTATCTTTTTCAGGTAATTGCATTGCA

FIG. 13C

110/173

FIG. 13D

111/173

ttgtttgcaagcagattacgcgagaaaaaggatctcaagaagatccttttgatctttttacgggggtctgacgctcagtg
 gaacgaaaaactcacgttaagggttttggtcatgattatcaaaaaaggatcttcacctagatccttttaataaaaaatgaagtttta
 aatcaatctaaagtatatatagtaaaacttggtctgacagttaccatgcttaacagtgaggccacctatctcagcgatctgtctatttc
 gttcatccatagttgcccgtgactcccgtcgtgtagataactacgatacgggagggctfiaccatctggccccagtgctgccaatgata
 ccgcgagacccacgctcacccggctccagatttatcagcaataaaccagccagccggaaaggccggagcgagaggtggtcct
 gcaactttatccgccctccatccagtcctatttaattgttgcgggaagctagagtagttcggccagttaatgtttggccaacggttgt
 tgccattgctacaggcgatcgtgtgtcagcctcgtctgttggtagtgccttcattcagctccgggtcccaacgatcaaggcgaggttac
 atgatccccatgtgtgtcaaaaaaagggttagctcttcggctcctcgatcgttgtaagaaagtgtggccgagtggttatcact
 catggttatggcagcactgcataattcttactgtcatgcccataccgttaagatgcttttctgtgactgggtgagtactcaaccaagtcatt
 ctgagaatagtgtatgcggcgaccgagttgctcttggccggcgtcaatacgggataataccggccacatagcagaactttaaaa
 gtgctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccggctgttgagatccagttcgatgtaaacccactcgt
 gcacccaactgatcttcagcatcttttactttaccagcgtttctgggtgagcaaaaacaggaaaggcaaaatgcccgaaaaaagg
 gaataaggcgacacggaaatgttgaatactcatactcttcttccaatatatttgaagcatttatcagggttattgtctcatgagcg
 gatacatatttgaatgtatttagaaaaataaacaataagggttcggcgacatttccccgaaaagtggccacctgacggccccctgt
 agcggcgcaftaagcgcggcggtgtgtgtgtacgcgacggtgacccgtacacttgccagcgccctagcgccccgctcctt
 cgccttcttcccttctcgtccacgttcggcggttccccgtcaagctctaaatcggggcatccttttaggggttccgatttagtgc
 tttagggcacctcgacccccaaaaaacttgattagggtgtgattcagtagtggccatcgccctgatagacgggttttcgcccc
 gacgttgagtgccacgttcttaataagtgactctgttccaaaactggacaacactcaacccctatctcgtctattcttttgatttataa
 gggatttggccgatttcggcctattgtgttaaaaaatgagctgatttaacaaaatttaacggaattttaacaaaaatataaacgttttac
 aattt

FIG. 13E

112/173

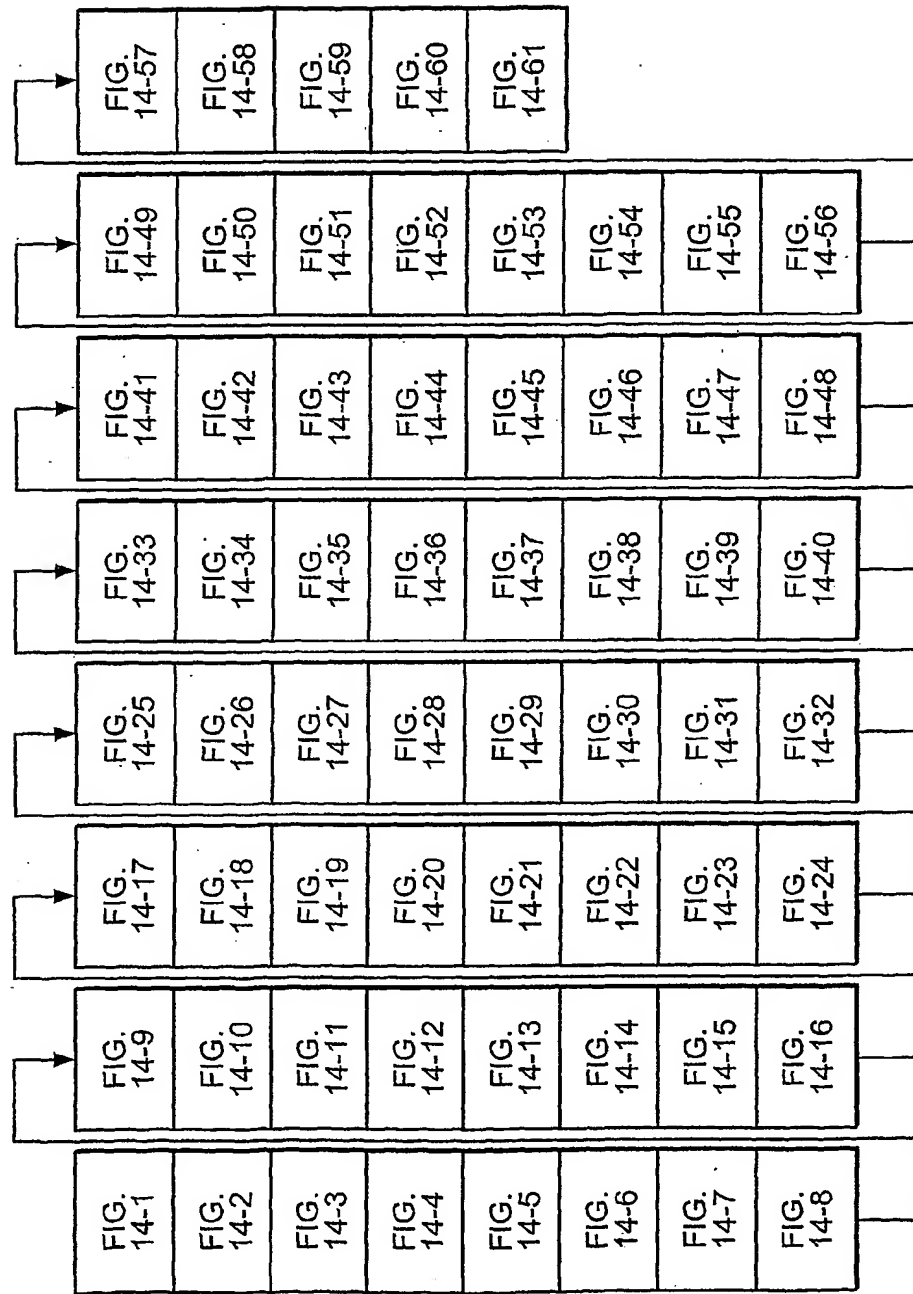


FIG. 14

pFLAG-CMV-5b-HDAC9a

7303 base pairs

Graphic map | Table by enzyme name

BstMCI	
AviII	PvuI BsiEI
BglI FspI	BsaOI
cccatcgccattcaggctgcgcaactgttggaaggcgatcggtgcgggcctcttcgctattacgccagctgg	EamI
base pairs	Eam1104I
gggtaagcgggtaagtccgacgcgttgacaacccttcccgctagccacgcccggagagcgataaatgcgggtcgacc	PvuII
1 to 75	113/173
Acc16I	
	BspCI
	Bsh1285I
	Ple19I
	Ksp632I
	NspBII

FIG. 14-1

114/173

cgaaggggatgtgctgcaaggcgattagttgggtaacgccagggtttcccagtcacgacgttgtaaaacg
base pairs
gctttccccctacacgacgttccgctaattcaaccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150

MscI

CfrI

SspI MluNI

EaeI

acggccagtgccaagctgatctaataatcgccattagccataattattcattggtatatagcataaaatcaa
base pairs
tgccggtcacgggttcgactagattagttataaccgggtaatcgggtataataagtaaccaatataatcgtagtttagtt
151 to 225

CfrI

EaeI

BalI

FIG. 14-2

115/173

MscI	SspBI
MluNI	Bsp1407I
EaeI	
BsrDI	
SspI	
tattggctattggccattggcatagcgttgatccatatcataaatatgtacatttataattggctcatgtccaacatt	
base pairs	
ataaccgataaaccggtaacgtatgcaacataggtatgtagtattatacatgtaaataataaccgagtacagggttgtaa	
226 to 300	
CfrI	BsrGI
BalI	

VspI	
PshBI	
HincII	SpeI
accgccatgttgacattgattattgactagttatttaataagtaaatcaattacgggggcatttagttcatagcccata	
base pairs	
tggcggtaacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatacaagtatcgggtat	
301 to 375	
HindII	AsnI
	AseI
	AcI

FIG. 14-3

HinII
AcyI
HincII

BstMCI
BglI BsaOI

tatggagttccgcgttacataacttacggttaaatggcccgctggcgaccgcccagcgacccccccggttgacg
base pairs
atacctcaaggcgcaatgtattgaatgccatttacggggcgaccgctggcggtcgctggggggggaactgc
376 to 450

HindII
Hsp92I
Msp17I

Bsh1285I
BsiEI

116/173

BsaHI
AatII
BbiII

BbiII
HinII
AcyI AatII

tcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttaccacctcataaatgcc
451 to 525

Msp17I
BsaHI
Hsp92I

FIG. 14-4

117/173

<p>BglI</p> <p>taaaactgcccaacttggcagtagacatcaagtgtatcatatgcccaagtcgcgccccctattgacgtcaatgacggtaaa base pairs attgacgggtgaaccgtcatgtagtccacatagtagtgcagggttcaggcgggggataaactgcaggttactgccattt 526 to 600</p>	<p>BbiII</p> <p>HinII</p> <p>AcylI AatII</p> <p>NdeI</p>	<p>FauNDI</p> <p>Msp17I</p> <p>BsaHI</p> <p>Hsp92I</p>
<p>tggcccgccctagcattatgccccagtagacattacgggagtttcctacttggcagtagacatctacgtattagtc base pairs accgggaggatcgtaatacgggtcatgtactggaatgccctcaaaggatgaaccgtcatgtagatgcataatcag 601 to 675</p>	<p>BstSNI</p> <p>SnaBI</p> <p>BsaAI</p> <p>Eco105I</p>	

FIG. 14-5

118/173

NcoI Bsp19I
 StyI BstDSI
 EcoT14I
 atcgctattaccatgggtgatgcggttttggcagtagaccaaattggcgtagcgggttgactcacggggattt
 base pairs
 tagcgataatggtaccactacgccaacacgtcatgtggttaccgcacacctatcgccaaactgagtgcctctaaa
 676 to 750
 BssT1I
 ErhI Eco130I
 DsaI MslI
 BblII
 HinII
 AccB1I
 AclI AatII
 BshNI
 ccaagtctccacccattgacgtcaatgggagttgttttggcaccacaaatcaacgggactttccaaaatgtcgt
 base pairs
 gggtcagaggtgggtaactgcagttaccctcaaaacacgtggttttagttgcccctgaaagggttttacagca
 751 to 825
 Msp17I
 BsaHI
 Hsp92I
 BanI
 Eco64I

FIG. 14-6

119/173

HincII
 Eco24I
 EcoICRI
 aataacccgccccgttgacgcaaatgggaggtaggcgtgtacgggtgggaggtctatataagca gagctcgttta
 base pairs
 ttattgggagggggcaactgcgtttaccggccatccgcacatgccaccctccagatatattcgt ctcgagcaaat
 826 to 900
 HindII
 Ecl136II
 Bbv12I
 AspHI
 Psp124BI

SacI
 FrlOI
 SstI
 BanII
 BsiHKAI
 AcsI
 ApoI
 BsiHKAI
 EagI
 XmaIII
 BstYI
 BspDI
 BcgI
 Eco32I
 CciNI
 Bsh1285I
 BstX2I
 BanIII
 PstI
 HindIII
 BstZI
 BstMCI
 MflI
 Bsa29I
 SfcI
 Ksp22I
 gtgaaccgtcagaattcaagcttgccggccagatctatcgatctgcaggatatcaccatgcacagtatgatcag
 base pairs
 cacttggcagtccttaagtctgaacggcggtctagatagctagcgtcctatagtggtacgtgtcatactagtc
 901 to 975
 EcoRI
 EaeI
 Eco52I
 BglII
 BscI
 BspXI
 BstSFI
 CfrI
 EclXI
 BsiEI
 BseCI
 Bsu15I
 EcoRV
 NotI
 BsaOI
 XhoII
 ClaI
 Bsp106I
 FbaI
 Alw21I

FIG. 14-7

	FriOI	CvnI	CvnI
	ECO24I	AOCI	AOCI
	BpmI	Bsu36I	Bsu36I
ctcagtggtgagtcagaagttcctgtgggcctggagcccatctcacctttagaccctaaggacagacctcag			
base pairs			
gagtcacctacacttcagtcctcaaggacacccggacctcggttagagtggaatctggattcctgtctggagtc			
976 to 1050			
	GsuI	Eco8II	Eco8II
	BanII	Bse2II	Bse2II

120/173

DsaI	DrdI	MfeI	Asp700I
gatgatgagcccggtggtggaccctgttgtccgtgagaagcaattgcagcaggaattacttcttatccagcagca			
base pairs			
ctactactacgggcaccacacctgggacacacaggcactcttcgttaacgctcgtcccttaatgaagaataggctcgtcgt			
1051 to 1125			
BstDSI	MunI	XmnI	

FIG. 14-8

121/173

AlwNI
gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
base pairs
cgttggttaggtcttcgtcgaagactatcgtctcaaagtctttgtcgtaactcttgaaactgtgccgtcgtggtccg
1126 to 1200

BlpI
CellII Eco57I EcoNI AlwNI
tcagcttcaggagcatatcaaggaaacttctagccataaaacagcaacaagaactcctagaaaaggagcagaaaact
base pairs
agtcgaagtcctcgtatagttccttgaagatcgggtattttgtcgtttgttcttgaggatcttttcctcgtcttga
1201 to 1275
Bsp1720I
Bpu1102I

FIG. 14-9

122/173

BpmI
ggagcagcagaggcaagaaacaggaagtagagaggcatcgagagaaacagcagcttcctcctctcagagggcaaaga
base pairs
cctcgtcgtctccggttcttgttccttcattctctccgtagcgtctcttgcgcgaaggagagagtcctccggtttct
1276 to 1350
GsuI
EcoNI

HindIII
tagaggacgagaaaggcagtggaagtacagaagtaaaagcag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccggtcaccggttcattgtcttcatttcgcttcgaaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 14-10

Van91I
AccB7I
aacgaaagacactccaactaatggaaaaaatcattccgtgagccgccatcccaagctctggtacacgggtgccca
base pairs
ttgcttttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt
1426 to 1500

Van91I
AccB7I
ccacacatcatggatcaaagctctccacccttagtggaacatctccatccctacaagtacacattaccaggagc
base pairs
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcattgtgtaattggtcctcg
1501 to 1575

Esp1396I
PflMI
123/173

FIG. 14-11

124/173

Alw21I	BstBI	
AspHI	Bpu14I	FriOI
	Csp45I	Eco24I
acaagatgcaaaaggatgatttcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaa		
base pairs		
tgttctacgttttcctactaaaggggaagctttttgacggagactcgggttgaacttccacgccagggtccaattt		
1576 to 1650		
BsiHKA I	SfuI	BanII
Bbv12I	NspV	
	LspI	

	BseRI	EcoNI
acagaaagtggcagagaggagaagcagagcccttactcagcggaaggatggaatgtgtcacttcattcaagaa		
base pairs		
tgtctttcaccggtctctccttctcgtcggggaatgagtcgcgccttcctacctttacaacagtgaaagtattctt		
1651 to 1725		

FIG. 14-12

Van91I	Van91I	
AccB7I	AccB7I	
BpmI PflMI		
gcgaatgtttgaggtgacagaatcctcagtcagtcagtagcagttctccaggctctgggccaggttcaccaacaatgg		
base pairs		
cgcttacaactccactgtcttaggagtcagtcagtcaggtccgagaccagggccaagtgggtttgttacc		
1726 to 1800		
GsuI		
	Esp1396I	
AlwNI	PflMI	125/173
Esp1396I		

gccaaactggaagtgttactgaaaatgagacttcgggtttgccccctaccctcatgccgagcaaatgggttcaca

base pairs

cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtagcggtcgtttaccacaagtgt

1801 to 1875

FIG. 14-13

BsaMI
Mva1269I
gcaacgcatttctaattcatgaagattccatgaacctgctaagtccttatacctctccttcttgcacattac
base pairs
cgttgcgtaagattaagtacttctaaggcttgacgattcagaaatatggagaggaacgggttgtaatg
1876 to 1950

BsmI RcaI
BspHI

ErhI
BstT1I

BstBI Acsi
Bpu14I
Csp45I

126/173

cttgggggttcccgcagtgccatcccagctcaatgctc gaattcactcaaaagcagaagtggtgagacgca
base pairs
gaaccccgaaggcggtcacggtagggtcgagttacgaag ctttaagtgaagtttcttcttcgtcttcacactctgcgt
1951 to 2025
EcoT14I

Esp3I

StyI
Eco130I

SfuI Bsp119I

NspV ApoI
LspI EcoRI

BsmBI

FIG. 14-14

127/173

gacgcttaggcaagggtggtccctctgcctgggcagtatggaggcagcatcccggcatcttccagccaccctcatgt
base pairs
ctgcgaatccggtccacaaggagacggaccggtcataccctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

MslI

tacttttagaggaaagccaccaccaacacagcagccaccagggtctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctccctttcgggtggtgtcgtcgggtccgagag gacgtcgtataataaactttcttgtttacgc
2101 to 2175

PstI

SfiI

BstSFI

FIG. 14-15

128/173

<p>HindIII</p> <p>acagcaaaagcttcttgtagctggtgagttcccttacatcctcagtcctcccttggaacaaagagagaatttc base pairs</p> <p>tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagagggaaccgttggtttctctcttaaag 2176 to 2250</p>	<p>Eco130I</p> <p>StyI</p> <p>EcoT14I</p> <p>ApoI</p>
<p>Asp718I</p> <p>Acc65I</p> <p>BshNI</p> <p>acctggcattagaggtacccacaaaattgccccgtcacagacccctgaaccgaaccagctctgcacctttgcctca base pairs</p> <p>tggaccgtaatctcccatgggtgtttaacgggggcagtgctgtgggacttggttggtcagacgtggaaacggagt 2251 to 2325</p>	<p>BssT1I</p> <p>ErhI</p> <p>AcSI</p> <p>BsgI</p>
<p>BanI</p> <p>KpnI</p> <p>AccB1I</p> <p>Eco64I</p>	

FIG. 14-16

129/173

Bpu1102I
 Alw21I Bsp1720I
 AspHI CelII
 gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagaataaccagcagca
 base pairs
 ctcgtagcaaccgagtcgaccagtaagtgtcggtcggttaagaacctcttcgtcttcggttatgggtcgtcgt
 2326 to 2400
 BsiHKA I PvuII
 Bbv12I B1pI MspAII
 NspBII
 MflI
 XhoII
 gatccacatgaacaaactgcttttcgaaatctattgaacaaactgaagcaaccaggcagtcaccttgaggaagcaga
 base pairs
 ctagggtgtacttgtttgacgaaagctttagataaacttggtgacttcggttggtccgtcagtggaactccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 BstBI
 Bpu14I
 Csp45I
 Eco57I
 SfuI Bsp119I
 NspV
 LspI

FIG. 14-17

130/173

EarI
 Eam1104I
 Asp700I
 Bbv16II
 BbsI Bsp143II
 ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
 base pairs
 ccttctcgaagtccccctgggtccgctacgtccctctctgtctcgcgggagatcacccgttgctcgatccctcgctgtc
 2476 to 2550
 XmnI Eco57I
 Ksp632I
 SapI
 BpiI HaeII
 BpuAI BstH2I

BcgI
 cagtgtgtgtggatgacacactgggacaagtggggctgtgaagggtcaaggagggaaccagtggaacagtgatga
 base pairs
 gtcacgaacacacactactgtgtgaccctgttcaacccccgacacttccagttcctccttggtcacctgtcactact
 2551 to 2625

FIG. 14-18

MflI Van91I
 XhoII AccB7I
 agatgctcagatccaggaaatggaatctggggagcaggctgttttatgcaacagcctttcctggaacccacgca
 base pairs
 tctacgagtcctaggtcctttaccttagacccctcgccgacgaaatacgttgctcgaaaggaccttgggtgcgt
 2626 to 2700
 BstYI Esp1396I
 BstX2I PflMI

131/173

PmaCI
 PmlI
 AflIII NspBII
 cacacgtgcgctctctgtgcgccaagctccgctggctgcggttgccatggatggattagagaaacacgctctcgt
 base pairs
 gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctaatctcttggcagagca
 2701 to 2775
 MslI Eco72I MspAII
 BsaAI
 BbrPI BsmBI

FIG. 14-19

132/173

EarI	BpmI	BsrDI	BpmI
Eam1104I			
ctccaggactcactcttcccctgctgcctctgttttacctcaccagcaatggaccgccccctccagcctggctc			
base pairs			
gaggtcctgagtgagaaggggacgagcgagacaaaaatggagtgggtcggttacctggcgggggaggtcggaccgag			
2776 to 2850			
GsuI	Ksp632I	GsuI	

XcmI
tgcaactggaattgcctatgaccccttgatgctgaaacaccagtgcgtttgtggcaattccaccaccacctga
base pairs
acgttgaccttaacggatactggggaactacgactttgtggtcacgcaaacacccgttaagggtgggtgggact
2851 to 2925

FIG. 14-20

133/173

<p>SphI BbuI</p> <p>gcatgctggacgacgaatacacagagtatctggtcacgactgcaagaactgggctgctaaataaatgtgagc gaattca base pairs</p> <p>cgtacgacctgcttatgtctcatagaccagtgctgacgttctttgacccgacgatttatttactactcg ctttaagt 2926 to 3000</p> <p>PaeI NspI</p>	<p>AcsI ApoI</p>
<p>BpmI</p> <p>aggtcgaaaagccagcctggaggaatacacagcttggttcattctgaacatcactcactgttgtagtggaaccaaccc base pairs</p> <p>tccagcttttcggtcggacctcctttatgtcgaacaagtaagacttgtagtgagtgacaacataccgtgggttggg 3001 to 3075</p> <p>GsuI</p>	<p>AccBII BshNI</p> <p>BanI Eco64I</p>

FIG. 14-21

134/173

ErhI
StyI Eco130I
EcoT14I
BstXI AlwNI
cctggacggacagaagctggaccccaggatactcctaggatgactctcaaaagttttttctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaggagtaatgggaac
3076 to 3150

BssT1I
AvtII
BlnI

BsaWI BsgI
tggaggacttggggtggacagtgacaccatttggaatgagctacactcgctcgggtgctgcacgcgtggttgg
base pairs
accacctgaacccccacctgtcactgtggtaaaccttactcgatgtgagcagggccacgacgtgcgtaccgacaacc
3151 to 3225

FIG. 14-22

	CvnI		CfrI
	AocI		DraII EaeI
	Bsu36I	Eco57I	
ctgtgtcatcgagctgggttccaaagtggcctcaggagagctgaagaatgggtttgctgtgtgagggccccctgg			
base pairs			
gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttacccaaacgacaacactccgggggacc			
3226 to 3300			
	Eco81I		EcoO109I
	Bse21I		

135/173

MscI	ErhI Eco130I
	BssT1I BstXI
	Eco57I MslI DsaI
ccatcacgctgaagaatccacagccatgggggttctgcttttttaattcagttgcaattaccggccaaatacttgag	
base pairs	
ggtagtgcgacttcttaggtgtcggtaccccaagacgaaaaaattaagtcaacgttaatggcggttttatgaactc	
3301 to 3375	
MluNI	EcoT14I
BalI	StyI BstDSI
	NcoI Bsp19I

FIG. 14-23

SspBI			
BspI407I	MslI	Asp700I	
ttatgctgacccagcatcctgtacatttcactcccatcgctatgatgaagggaactttttccctggcagtgaggc			
base pairs			
aatacgactggggtcgtaggacatgtaaagtgaggtaggatactacttcccttgaaaaaggaccgtcacctcg			
3451 to 3525			
BsrGI			XmnI

FIG. 14-24

FriOI	FriOI	BstYI
Eco24I	Eco24I	XhoII
cccaaatgaggttcggttatttcttagagccccacttttatttgtatctttcaggtaatgcatgca ggatc		BsrDI
base pairs		
gggtttactccaagccaaataaagaaatctcggggtgaaaataaacatagaaaagtcattaaacgtaacgt cctag		
3526 to 3600		
BanII	BanII	BamHI
		BstI
		MflI

137/173

Acc65I	AvaI BcoI
BanI Eco64I	MflI Eco88I PspAlI
BstX2I Asp718I	XhoII Cfr9I SmaI MslI
cgtaccagattacaaggacgacgatgacaaagtagat ccgggtggcatccctgtgacccctccccagtgccctct	
base pairs	
gccatgggtctaattgttcctgctgctactgttcatcta gggcccaccgtagggagacactggggagggtcacggaga	
3601 to 3675	
BshNI	BstYI Ama87I
BsaWI KpnI	BstX2I BsoBI
AccB1I	XmaI PspAI

FIG. 14-25

FIG. 14-26

DraII	BpmI BsgI	
gtagggcctgcggtctattcgggaaccaagctggagtgagtggcacaaatcttggtcactgcaatctccgcc		
base pairs		
catccggagcggcccccagataagcccttggttcgacctcacgtcaccggtttagaacggagtgacgttagagggcgg		
3826 to 3900		
EcoO109I	GsuI	
		139/173
	BcoI	NspI BlpI
	Ama87I	PaeI Mph1103I
	BcgI	Ppu10I EcoT22I
tcctgggttcaagcgaattctcctgcctcagcctcccagttgttggtccaggcatgaccaggctcagc		
base pairs		
aggacccaagtctcgctaagaggacggagtcggagggctcaacaaccctaagggtccgtactggtccgagtcg		
3901 to 3975		
	Eco88I	BbuI Zsp2I CelII
	BsoBI	SphI Bsp172
		NsiI Bpu1I

FIG. 14-27

140/173

		MscI	
		MluNI	
	Esp3I	EaeI	BsaI
taatttttggttttttggtagagacggggtttcaccatatattggccagggtggtctccaactcctaattctcaggtg			
base pairs			
attaaaaacaaaaaaccatctctgtgccccaaagtgggtataaccgggtccgaccagaggttgaggatttagagtcac			
3976 to 4050			
	BsmBI	CfrI	Eco31I
		BalI	
0I			
02I			
	Eco130I		
	StyI		
	EcoT14I	BstXI	
atctaccacaccttggcctcccaaatgctgggttacaggcgtgaaccactgctcccttccctgtccttctgatt			
base pairs			
tagatgggtggaaccggagggtttaacgaccctaattgtccgcacttggtgacgaggggaaggacaggaagactaa			
4051 to 4125			
	Bst1I		
	ErhI		

FIG. 14-28

BbiII	NcoI Eco130I BsrFI PflMI
HinII	StyI DsaI AgeI Bse118I
AcyI AatII	EcoT14I BsaWI AccB7I
DraI	ttaaaataataaccagcaggaggtccagacacagcataggctacctgcccacccgggtgggacat
	base pairs
	aattttattgatattggtcgtccctcctgcaggtctgtgtcgatccgatggacgggtaccgggtggccaccctgta
	4126 to 4200
Msp17I	Bst1I BssAI Esp1396I
BsaHI	ErhI BstDSI PinAI Van91I
Hsp92I	BspMI Bsp19I Cfr10I

141/173

ttgagttgcttgcttggaactgtcctctcatgcgttgggtccactcagtagatgcctgttggaattgggtacgcgg	EaeI
base pairs	
aactcaacgaacgaaccgtgacaggagagtagtcgcaaccagggtgagtcattacggacaacttaaccatgcgcc	
4201 to 4275	CfrI

FIG. 14-29

142/173

AlwNI
ccagcttctgtggaatgtgtgcagttaggggtgtggaagtccccagggtccccagcaggcagaagtatgcaaag
base pairs
ggtcgaagacacaccttacacacagtcacatccccacacctttcaggggtccgaggggtcggtcgtcttcatacgttttc
4276 to 4350

NspI
PaeI Mph1103I
Ppu10I EcoT22I SexAI
catgcatctcaattagtcagcaaccagggtgtggaagtccccagggtccccagcaggcagaagtatgcaaagca
base pairs
gtacgtagagtttaatcagtcgttgggtccacaccttttcaggggtccgaggggtcggtcgtcttcatacgttttcgt
4351 to 4425
BbuI Zsp2I
SphI
NsiI

FIG. 14-30

143/173

NspI
PaeI Mph1103I
Ppu10I EcoT22I
tgcatctcaattagtcagcaaccatagtcgcccccctaactccgcccataccgcccctaactccgcccagttccg
base pairs
acgtagagttaatcagtcggttggtatcagggcggggattgagggcgggtagggcggggattgagggcgggtcaaggc
4426 to 4500
BbuI Zsp2I
SphI
NsiI

NcoI Bsp19I
StyI BstDSI
EcoT14I
BglI
ccattctccgcccctggctgactaatTTTTTTTatttatgcagagggccgagccctcggcctctgagctat
base pairs
gggtaagagggcggtaccgactgattaaaaaaaaataacgtctcggctccggcgaggccggagactcgata
4501 to 4575
BssT1I
ErhI Eco130I
DsaI
SfiI

FIG. 14-31

144/173

SseBI AvrII Ama87I
 Eco147I BlnI Eco88I BseRI
 StuI BstXI AvaI BsoBI
 BseRI
 tccagaagtagtgaggaggttttttggaggcctaggcttttgcaaaaagctc ctcgaggaaactgaaaaaccaga
 base pairs
 aggtcttccatcactcctccgaaaaaacctccggatccgaaaacgttttttcgag gagctccttgacttttttggtct
 4576 to 4650

AatI StyI XhoI BcoI
 Pme55I ErhI Sfr274I
 EcoT14I Eco130I PaeR7I

SfcI ApoI
 aagttaattccctatagtgagtcgtatttaaatcgttaaatcatggtcatagctgtttcctgtgtgaaattgttattc
 base pairs
 ttcaattaagggatattcactcagcataatttaagcatttagtaccagtagtcgacaaaaggacacactttaacaatag
 4651 to 4725

BstSFI
 AcsI

FIG. 14-32

AccBSI	AccB1I	
BsrBI	BshNI	
cgctcacaaattccacacaacatacgagccggaagcataaagtgtaaagcctgggggtgcctaataatgagtgagctaac		
base pairs		
gcgagtgttaagggtgtgtgtatgctggccttcgtatttcacatttcggacccccacggattactcactcgattg		
4726 to 4800		
BstD102I	BanI	
	Eco64I	
		145/173
VspI	VspI	
PshBI	MspA1I	
	PvuII PshBI	
	EaeI	
tcacattaattgcggttcgctcactgcccgtttccagtcgggaaacctgtcgtgccagctgcattaatgaatcg		
base pairs		
agtgtaatgaacgacgagtgacgggcgaaaggtcagccctttggacagcacgggtcgacgtaattacttagc		
4801 to 4875		
AsnI	NspBII	
AseI	AsnI	
	AseI	
	CfrI	

FIG. 14-33

146/173

Eam1104I
 BstH2I
 Bsp143II
 gccaacgcgcgggagagcggtttgcgtattgggcgctcttcgcgttcctcgctcactgactcgctgcgctcgg
 base pairs
 cggttgcgcgcgccctctccgccaacgcataaacccgcgagaaaggcgagtgactgagcgacgcgagcc
 4876 to 4950

HaeII EarI
 SapI
 Ksp632I

BstMCI
 BsaOI
 AccBSI
 BsrBI
 tcggtcggctgcgcgcgcgtatcagctcactcaaaaggcggttaatacggttatccacagaatcaggggataacg
 base pairs
 agcaagccgcgcgcgcgtcgcgcatagtcgcgtgagtttcgcgccattatgcccaatagggtgtcttagtccccctattgc
 4951 to 5025
 Bsh1285I
 BsiEI
 BstD102I

FIG. 14-34

147/173

NspI
BspLU11I
caggaaagaacatgtgagcaaaaggccagcaaaaggccaggaaaccgtaaaaaggccgcttgctggcgtttttcc
base pairs
gtcctttcttgtaactcgttttccggtcgtttccggtccttggcatttttccggcgcaacgacccgcaaaaagg
5026 to 5100
AflIII

DrdI
ataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactat
base pairs
tatccgaggcgggggactgctcgtagtgttttttagctcgagttcagtcctccacggctttgggctgtcctgata
5101 to 5175

FIG. 14-35

148/173

BsiI BsaWI
aaagataccaggcgtttccccctggaagctccctcgtgcgctctcctgttccgaccctgccgcttaccggatacc
base pairs
tttctatggtccgcaaaaggggaccttcgaggagcacgcgagaggaacaaggctgggacggcggaatggcctatgg
5176 to 5250

BssSI

BstH2I SfiI
Bsp143II
tgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcagttcgggtgtagg
base pairs
acaggcgaaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacatccatagagtcgaagccacatcc
5251 to 5325

HaeII BstSFI

FIG. 14-36

BsiHKAI NspBII
 Alw44I BstMCI
 VneI Bbv12I BsaOI BsaWI
 tcgttcggtccaagctgggctgtgtgcacgaaccccccggttcagcccgaccgctgcgccttatccggtaactatc
 base pairs
 agcaagcgaggctcgacccgacacacgtgcttggggggcaagtcgggctggcgacgcggaataggccattgatag
 5326 to 5400
 ApaLI Bsh1285I
 AspHI BsiEI
 Alw21I MspAII

149/173

AlwNI
 gtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagcagagcga
 base pairs
 cagaactcagggtgggccattctgtgctgaatagcggtgaccgtcgtcggtgaccattgtcctaatacgtctcgct
 5401 to 5475

FIG. 14-37

150/173

SfCI
ggtagtagcggtgctacagagttcttgaagtggcctaactacggctacactagaagaacagtatttggta
base pairs
ccatacatccgcccacgatgtctcaagaacttcaccaccggattgatgccgatgtgatcttcttgcataaaccat
5476 to 5550

BstSFI

Eco57I
tctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaaaaccaccgctg
base pairs
agacgcgagacgacttcgggtcaatggaagccttttctcaaccatcgagaactaggccgttctgttggggcgac
5551 to 5625

NspBII

MspAII

FIG. 14-38

MflI MflI
 XhoII XhoII
 gtagcggtaggtttttgttgcaagcagcagattacgcgcagagaaaaaaggatctcaagaagatcctttgatct
 base pairs
 catcgccaccacaaaaaacaacgttcgtcgtctaatacgcggtccttttttccctagagttcttctaggaactaga
 5626 to 5700

BstYI BstYI
 BstX2I BstX2I

151/173

RcaI MflI
 XhoII
 tttctacgggtctgacgctcagtggaaacgaaaactcacgttaagggttttggtcatgagattatcaaaaagga
 base pairs
 aaagatgccccagactgcgagtcaccttgcttttgagtgcgaattccctaaaaccagtactctaatagtttttcct
 5701 to 5775

BspHI BstYI
 BstX2I

FIG. 14-39

152/173

MflI DraI
XhoII DraI
tcttcacccatagatcccttttaaattaaaaatgaagttttaaatcaatcctaagatatatgagtaaacttgggtctg
base pairs
agaagtggatctaggaaaatttaatttttacttcaaaaatttagttagatttcatatatactcatttgaaccagac
5776 to 5850
BstYI
BstX2I

AccB1I
BshNI
acagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatagttgcctgac
base pairs
tgtcaatgggttacgaaattagtcactccgtggatagatcgctagacagataaagcaagtaggtatcaacggactg
5851 to 5925
BamI
Eco64I

FIG. 14-40

153/173

Eam1105I
 AspEI
 BsrDI
 tccccgtcgtgtagataaactacgatacgggagggttaccatctggcccagtgctgcaatgataccgcgagacc
 base pairs
 aggggcagcacatctattgatgctatgccctcccgaatggtagaccgggtcacgacgttactatggcgctctggg
 5926 to 6000
 EclHKL
 AhdI

Cfr10I
 BsaI BssAI BpmI BglI
 cacgtcacccggctccagatttatcagcaataaaccagccggaaggccgagcgagaagtggctcctgcaa
 base pairs
 gtgcgagtggccgaggtctaaatagtcgttatttggtcgggtcccggtcttcaccaggacgtt
 6001 to 6075
 Eco31I BsrFI GsuI
 Bse118I

FIG. 14-41

154/173

VspI
 PshBI
 cttatccgcctccatccagtcctataattgttgccgggaagctagagtaagtagttcgccagttaatagtttgc
 base pairs
 gaaataggcgggtaggtcagataattaacaacggcccttcgatctcattcatcaagcgggtcaattatcaaacg
 6076 to 6150
 AsnI
 AseI

AviII
 FspI
 gcaacggtgttgccattgctacaggcatcggtgtcacgctcgctgttggtatggcttcattcagctccggtt
 base pairs
 cgttgcaacaacggtaacgatgtccgtagcaccacagtcgagcagcaaacccataccggaagtaagtcgaggccaa
 6151 to 6225
 Acc16I
 BsrDI
 Psp1406I
 BstSFI
 SfiI
 MslI
 BsaWI

FIG. 14-42

BsiEI
PvuI
BstMCI
BsaOI

cccaacgatcaaggcgagttacatgatcccccatgttggtgcaaaaaagcggtagctccttcggtcctccgatcg
base pairs
gggttgctagttccgctcaatgtactagggggtacaacacgttttttcgccaatcgaggaagccaggaggctagc
6226 to 6300

BspCI
Bsh1285I
Ple19I

155/173

MslI

EaeI

ttgtcagaagtaagttggccgcagtggttatcactcatgggttatggcagcactgcataattcttactgtcatgc
base pairs
aacagtcttcatccaacccggcggtcaccaatagtgagtaccaataaccgtcgtgacgtattaagagaatgacagtagc
6301 to 6375

CfrI

FIG. 14-43

Acc113I	BstMCI	
	BsaOI	
Eco255I		
catccgtaagatgcttttctgtgactgggtgagtactcaaccaagtcattctgagaatagtgatcgggcgaccga		
base pairs		
gtaggcattcttacgaaaagacactgaccactcatgagttgggttcagtaagactcttatacacatacgccgctggct		
6376 to 6450		
ScaI	Bsh1285I	
	BsiEI	
		156/173
BbiII	Alw21I	
HinII	AspHI	
BcgI	DraI	
gttgctcttgcccggcggtcaatacgggataataccgcccacatagcagaactttaaaagtgctcatcattggaa		
base pairs		
caacgagaacggggccgcaggttatgccctattatggcgcggtgtatcgctcttgaaattttcacgagtagtaacctt		
6451 to 6525		
Msp17I	BsiHKA1	
BsaHI	Bbv12I	
Hsp92I		

FIG. 14-44

XmnI

Psp1406I

aacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagttcgatgtaacccactcgtgcac

base pairs

ttgcaagaagccccgcttttgagagttcctagaaatggcgacaactctaggtcaagctacattgggtgagcacgtg

6526 to 6600

Asp700I

MflI

XhoII

NspBII

XhoII

MflI

BssSI

Alw44I

VneI

BstYI

BstX2I

MspAII

BstYI

BstX2I

ApalI

BsiI

AspHI

157/173

Bbv12I

BsiHKAI

ccaaatgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaaacaggaaggcaaaatgccgcaa

base pairs

ggttgactagaagtcgtagaaaaatgaaagtgggtcgaaagaccactcgtttttgtccttccggttttacggcggtt

6601 to 6675

Alw21I

Eco57I

FIG. 14-45

158/173

MslI
 EarI
 Ham1104I SspI
 aaaaggaataagggcgacacgggaaatggtgaataactcatactcttcctttttcaatatattgaagcatttattc
 base pairs
 tttcccttattcccgctgtgcctttacaacttatgagatgagaaggaaaaagttataataaacttcgtaaatag
 6676 to 6750
 Ksp632I

AccBSI
 RcaI BsrBI
 agggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaacaataaggggttccgcgcacat
 base pairs
 tcccaataacagagtagtccgctatgtataaaacttacataaatctttttattgtttatccccaaggcgcgtgta
 6751 to 6825
 BspHI BstD102I

FIG. 14-46

SfcI

ttccccgaaaagtgccacacctgacggcgccctgtagcggcgcatattaagcggcggggtgtggttggttacgcgcagcgg
 base pairs
 aaggggcttttcacgggtggactgcgcgggacatgcgcgcgtaattcgcgcgcgccacacacccaatgcgcgtcgc
 6826 to 6900

BstSFI

159/173

AccBSI

BstH2I HaeII BstD102I BsrFI
 Bsp143II BsrBI BssAI
 MroNI

tgaccgctacacttgccagcgccctagcggccgctcctttcgcgtttctcccttctccttctcgcacggttcgcgcg
 base pairs
 actggcgatgtgaacgggtcgcgggacgcgggcgaggaagcgaagaaagggaagagcgggtgcaagcggc
 6901 to 6975

HaeII Bsp143II NgoAIV
 BstH2I BstH18I NgomI

FIG. 14-47

160/173

NaeI
gctttcccgtaagctctaaatcggggcatccctttagggtccgatttagtgctttacggcacctcgacccca
base pairs
cgaaggggcagttcgagatttagccccgtagggaaatcccaaggctaataatcacgaaatgccgtggagctgggggt
6976 to 7050

AccBII
BshNI

BanI
Eco64I

Cfr10I

BsaAI
aaaaacttgattagggtgatggttcacgtagtggggccatgccctgatagacgggttttccgcccttgacgttgg
base pairs
tttttgaactaatcccactaccaagtgcatacccggtagcgggactatctgccaaaaagcgggaaactgcaacc
7051 to 7125

DraIII

FIG. 14-48

agtcacggttctttaatagtggaactctgttccaactggaacaacactcaaccctatctcgggtctattcttttg
base pairs
tcaggtgcaagaattatcacctgagaacaagggttgacctgtgtgagttgggatagagccagataaagaaaac
7126 to 7200

atttataagggattttgccgatttcggcctatttggttaaaaaatgagctgatttaacaaaaatttaacgcgaatt
base pairs
taaataattccctaaaaacgggctaagccggataaccaattttttactcgactaaattgtttttaaatggcgcttaa
7201 to 7275

ApoI ApoI

161/173

Acsi Acsi

SspI Psp1406I
ttaacaaaatatttaaacggtttacaattt base pairs
aattgttttataatttgcaaatgttaaa 7276 to 7303

FIG. 14-49

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence
AatI	2	3446 4606	agg/cct <u>More info</u>
AatII	5	451 504 587 773 4154	gacgt/c <u>More info</u>
Acc113I	1	6408	agt/act <u>More info</u>
Acc16I	2	21 6150	tgc/gca <u>More info</u>
Acc65I	3	2264 3434 3602	g/ gtacc <u>More info</u>
AccB1I	8	791 2264 3065 3434 3602 4779	g/ gyrcc <u>More info</u>
		5876 7036	
AccB7I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg <u>More info</u>
AccBSI	4	4730 4971 6772 6936	
Ac1NI	1	326	gagcgg <u>More info</u>
AcSI	7	912 1990 2244 2994 4679 7260	a/ ctagt <u>More info</u>
		7271	r/ aatty <u>More info</u>
AcylI	6	448 501 584 770 4151 6465	gr/cgyc <u>More info</u>
Afl1III	2	2702 5035	a/ crygt <u>More info</u>
AgeI	1	4188	a/ ccggt <u>More info</u>
AhdI	2	3754 5928	gacnnn/ngtc <u>More info</u>
Alw21I	6	894 1576 2330 5353 6514 6599	gwgcw/c <u>More info</u>
Alw44I	2	5349 6595	g/ tgcac <u>More info</u>

162/173

FIG. 14-50

163/173

AlwNI	6	1147	1273	1775	3091	4282	5451	cagnnn/ctg	More info
Ama87I	3	3638	3934	4629				c/ ycgrg	More info
AocI	3	1034	1046	3256				cc/ tnagg	More info
Apal	1	3806						gggcc/c	More info
ApalI	2	5349	6595					g/ tgcac	More info
ApoI	7	912	1990	2244	2994	4679	7260	r/ aatty	More info
		7271							
AseI	4	334	4806	4865	6100			at/ taat	More info
AsnI	4	334	4806	4865	6100			at/ taat	More info
Asp700I	4	1107	2481	3506	6527			gaann/nnttc	More info
Asp718I	3	2264	3434	3602				g/ gtacc	More info
AspEI	2	3754	5928					gacnnn/nngtc	More info
AspHI	6	894	1576	2330	5353	6514	6599	gwgwc/c	More info
AvaI	3	3638	3934	4629				c/ ycgrg	More info
AviII	2	21	6150					tgc/gca	More info
AvrII	2	3109	4607					c/ ctagg	More info
BalI	4	184	238	3300	4018			tgg/cca	More info
BamHI	1	3596						g/ gatcc	More info
BanI	8	791	2264	3065	3434	3602	4779	g/ gyrcc	More info
		5876	7036						
BanII	6	894	1017	1623	3526	3558	3806	grgcy/c	More info
BanIII	1	939						at/ cgat	More info
BbiII	6	448	501	584	770	4151	6465	gr/cgyc	More info

FIG. 14-51

BbrPI	1	2705	cac/gtg	<u>More info</u>
BbsI	2	2512 3820	gaagac	<u>More info</u>
BbuI	4	2930 3959 4354 4427	gcatg/c	<u>More info</u>
Bbv12I	6	894 1576 2330 5353 6514 6599	gwgw/c	<u>More info</u>
Bbv16II	2	2512 3820	gaagac	<u>More info</u>
BcgI	4	941 2556 3925 6455	cgannnnntgc	<u>More info</u>
BclI	1	969	t/ gatca	<u>More info</u>
BcoI	3	3638 3934 4629	c/ ycgrg	<u>More info</u>
BglI	5	14 417 538 4560 6048	gccnnnn/nggc	<u>More info</u>
BglII	2	932 3409	a/ gatct	<u>More info</u>
BlnI	2	3109 4607	c/ ctagg	<u>More info</u>
BlpI	3	1200 2337 3970	gc/tnagc	<u>More info</u>
BpiI	2	2512 3820	gaagac	<u>More info</u>
BpmI	9	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
Bpu1102I	3	3701 3863 6018	gc/tnagc	<u>More info</u>
Bpu14I	3	1200 2337 3970	tt/cgaa	<u>More info</u>
BpuAI	2	1603 1988 2423	gaagac	<u>More info</u>
Bsa29I	1	2512 3820	at/ cgat	<u>More info</u>
BsaAI	3	939	yac/gtr	<u>More info</u>
BsaHI	6	666 2705 7077	gr/cgyc	<u>More info</u>
		448 501 584 770 4151 6465		

164/173

FIG. 14-52

165/173

BsaI	3	3380	4031	6000	ggtctc	More info
BsaMI	1	1886			gaatgc	More info
BsaOI	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BsaWI	6	3200	3599	4188 5241 5388 6219	w/ ccgww	More info
BsCI	1	939			at/ cgat	More info
Bse118I	3	4188	6008	6972	r/ ccggy	More info
Bse21I	3	1034	1046	3256	cc/ tnagg	More info
BseCI	1	939			at/ cgat	More info
BseRI	4	1337	1671	4593 4631	gaggag	More info
BsgI	3	2315	3212	3868	gtgcag	More info
Bsh1285I	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BshNI	8	791	2264	3065 3434 3602 4779	g/ gyrc	More info
		5876	7036			
BsiEI	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BsiHKAI	6	894	1576	2330 5353 6514 6599	gwgcw/c	More info
BsiI	2	5213	6597		ctcgtg	More info
BsmBI	3	2023	2773	4001	cgtctc	More info
BsmI	1	1886			gaatgc	More info
BsoBI	3	3638	3934	4629	c/ ycgrg	More info
Bsp106I	1	939			at/ cgat	More info
Bsp119I	3	1603	1988	2423	tt/cgaa	More info
Bsp120I	1	3802			g/ ggccc	More info
Bsp1407I	2	270	3471		t/ gtaca	More info

FIG. 14-53

166/173

Bsp143II	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
Bsp1720I	3	1200	2337	3970			gc/tnagc	<u>More info</u>
Bsp19I	5	686	3324	3424	4178	4514	c/ catgg	<u>More info</u>
BspCI	2	42	6298				cgat/cg	<u>More info</u>
BspDI	1	939					at/ cgat	<u>More info</u>
BspHI	3	1891	5755	6763			t/ catga	<u>More info</u>
BspLUI1I	1	5035					a/ catgt	<u>More info</u>
BspMI	2	1913	4178				acctgc	<u>More info</u>
BspXI	1	939					at/ cgat	<u>More info</u>
BsrBI	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BsrDI	5	245	2827	3594	5987	6169	gcaatg	<u>More info</u>
BsrFI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BsrGI	2	270	3471				t/ gtaca	<u>More info</u>
BssAI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BssSI	2	5213	6597				ctcgtg	<u>More info</u>
BssT1I	11	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3681	4060	4178	4514	4607		
BstBI	3	1603	1988	2423			tt/cgaa	<u>More info</u>
BstD102I	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BstDSI	6	686	1062	3324	3424	4178 4514	c/ crygg	<u>More info</u>
BstH2I	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
BstI	1	3596					g/ gatcc	<u>More info</u>

FIG. 14-54

BstMCI	7	42 424 928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BstSFI	8	944 2144 3824 4662 5300 5491	c/ tryag	<u>More info</u>
		6169 6854		
BstSNI	1	666	tac/gta	<u>More info</u>
BstX2I	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstXI	3	3076 3325 4077	ccannnnn/ntgg	<u>More info</u>
BstYI	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstZI	1	925	c/ ggccg	<u>More info</u>
Bsu15I	1	939	at/ cgat	<u>More info</u>
Bsu36I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
CciNI	1	925	gc/ggccgc	<u>More info</u>
CelII	3	1200 2337 3970	gc/tnagc	<u>More info</u>
Cfr10I	3	4188 6008 6972	r/ ccggy	<u>More info</u>
Cfr9I	1	3638	c/ ccggg	<u>More info</u>
CfrI	9	152 182 236 925 3298 4016 4273	y/ ggccr	<u>More info</u>
		4874 6316		
ClaiI	1	939	at/ cgat	<u>More info</u>
Csp45I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
CvnI	3	1034 1046 3256	cc/ tnagg	<u>More info</u>

167/173

FIG. 14-55

DraI	4	4127	5794	5813	6505	ttt/aaa	More info
DraII	3	3291	3802	3829		rg/gnccy	More info
DraIII	1	7080				cacnnn/gtg	More info
DrDI	3	1076	5143	7124		gacnnnn/nngtc	More info
Dsai	6	686	1062	3324	3424 4178 4514	c/ crygg	More info
EaeI	9	152	182	236	925 3298 4016 4273	y/ ggccr	More info
		4874	6316				
EagI	1	925				c/ ggccg	More info
Eam1104I	5	58	2482	2793	4918 6722	ctcttc	More info
Eam1105I	2	3754	5928			gacnnn/nngtc	More info
EarI	5	58	2482	2793	4918 6722	ctcttc	More info
Ecl136II	1	892				gag/ ctc	More info
EclHKI	2	3754	5928			gacnnn/nngtc	More info
EclXI	1	925				c/ ggccg	More info
Eco105I	1	666				tac/gta	More info
Eco130I	11	686	1950	2226	3109 3324 3424	c/ cwwgg	More info
		3681	4060	4178	4514 4607		
Eco147I	2	3446	4606			agg/cct	More info
Eco24I	6	894	1017	1623	3526 3558 3806	grgcy/c	More info
Eco255I	1	6408				agt/act	More info
Eco31I	3	3380	4031	6000		ggtctc	More info
Eco32I	1	952				gat/ atc	More info
Eco52I	1	925				c/ ggccg	More info

168/173

FIG. 14-56

Eco57I	7	1210 2446 2488 3271 3314 5567 6615	ctgaag	<u>More info</u>
Eco64I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	<u>More info</u>
Eco72I	1	2705	cac/gtg	<u>More info</u>
Eco81I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
Eco88I	3	3638 3934 4629	c/ ycgrg	<u>More info</u>
EcoICRI	1	892	gag/ ctc	<u>More info</u>
EcoNI	3	1259 1338 1684	cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291 3802 3829	rg/gnccy	<u>More info</u>
EcoRI	3	912 1990 2994	g/ aattc	<u>More info</u>
EcoRV	1	952	gat/ atc	<u>More info</u>
EcoT14I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	<u>More info</u>
EcoT22I	3	3961 4356 4429	atgca/t	<u>More info</u>
ErhI	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	<u>More info</u>
Esp1396I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	<u>More info</u>
Esp3I	3	2023 2773 4001	cgtctc	<u>More info</u>
FauNDI	1	560	ca/ tatg	<u>More info</u>
FbaI	1	969	t/ gatca	<u>More info</u>
FriOI	6	894 1017 1623 3526 3558 3806	grgcy/c	<u>More info</u>
Fspi	2	21 6150	tgc/gca	<u>More info</u>

169/173

FIG. 14-57

170/173

GsuI	9	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
HaeII	5	3701 3863 6018	rgcgc/y	<u>More info</u>
HinII	6	2519 4913 5283 6922 6930	gr/cgyc	<u>More info</u>
HincII	3	448 501 584 770 4151 6465	gty/rac	<u>More info</u>
HindII	3	311 446 842	gty/rac	<u>More info</u>
HindIII	3	311 446 842	a/ agctt	<u>More info</u>
Hsp92I	6	918 1394 2183	gr/cgyc	<u>More info</u>
KpnI	3	448 501 584 770 4151 6465	ggtac/c	<u>More info</u>
Ksp22I	1	2268 3438 3606	t/ gatca	<u>More info</u>
Ksp632I	5	969	ctcttc	<u>More info</u>
LspI	3	58 2482 2793 4918 6722	tt/cgaa	<u>More info</u>
MfeI	1	1603 1988 2423	c/ aattg	<u>More info</u>
MflI	12	1091	r/ gatcy	<u>More info</u>
MluNI	4	932 2400 2634 3409 3596 3634	tgg/cca	<u>More info</u>
Mph1103I	3	5676 5687 5773 5785 6553 6570	atgca/t	<u>More info</u>
MronI	1	184 238 3300 4018	g/ ccggc	<u>More info</u>
MscI	4	3961 4356 4429	tgg/cca	<u>More info</u>
MslI	10	6972	caynn/nnrtg	<u>More info</u>
Msp17I	6	184 238 3300 4018	gr/cgyc	<u>More info</u>
MspA1I	7	691 2094 2703 3323 3489 3651	cmg/ckg	<u>More info</u>
		3698 6180 6339 6698		
		448 501 584 770 4151 6465		
		71 2341 2731 4859 5377 5622 6563		

FIG. 14-58

171/173

MunI	1	1091		c/ aattg	More info
MvaI269I	1	1886		gaatgc	More info
NaeI	1	6974		gcc/ggc	More info
NcoI	5	686 3324 3424 4178 4514		c/ catgg	More info
NdeI	1	560		ca/ tatg	More info
NgoAIV	1	6972		g/ ccggc	More info
NgomI	1	6972		g/ ccggc	More info
NotI	1	925		gc/ggccgc	More info
NsiI	3	3961 4356 4429		atgca/t	More info
NspBII	7	71 2341 2731 4859 5377 5622 6563		cmg/ckg	More info
NspI	5	2930 3959 4354 4427 5039		rcatg/y	More info
NspV	3	1603 1988 2423		tt/cgaa	More info
PaeI	4	2930 3959 4354 4427		gcatg/c	More info
Paer7I	1	4629		c/ tcgag	More info
PflMI	6	1445 1482 1775 1796 2644 4191		ccannnn/ntgg	More info
PinAI	1	4188		a/ ccggt	More info
Ple19I	2	42 6298		cgat/cg	More info
PmaCI	1	2705		cac/gtg	More info
Pme55I	2	3446 4606		agg/cct	More info
PmlI	1	2705		cac/gtg	More info
Ppu10I	3	3957 4352 4425		a/ tgcac	More info
PshBI	4	334 4806 4865 6100		at/ taat	More info
Psp124BI	1	894		gagct/c	More info
Psp1406I	3	6154 6527 7291		aa/cggt	More info

FIG. 14-59

172/173

PspAI	1	3638	c/ ccggg	More info
PspALI	1	3640	ccc/ggg	More info
PspOMI	1	3802	g/ ggccc	More info
PstI	2	948 2148	ctgca/g	More info
PvuI	2	42 6298	cgat/cg	More info
PvuII	3	71 2341 4859	cag/ctg	More info
RcaI	3	1891 5755 6763	t/ catga	More info
SacI	1	894	gagct/c	More info
SapI	2	2483 4918	gctcttc	More info
ScaI	1	6408	agt/act	More info
SexAI	1	4373	a/ ccwgg	More info
SfcI	8	944 2144 3824 4662 5300 5491 6169 6854	c/ tryag	More info
SfiI	1	4560	ggccnnnn/nggcc	More info
Sfr274I	1	4629	c/ tcgag	More info
SfuI	3	1603 1988 2423	tt/cgaa	More info
SmaI	1	3640	ccc/ggg	More info
SnaBI	1	666	tac/gta	More info
SpeI	1	326	a/ ctagt	More info
SphI	4	2930 3959 4354 4427	gcatg/c	More info
SseBI	2	3446 4606	agg/cct	More info
SspBI	2	270 3471	t/ gtaca	More info
SspI	5	179 226 3768 6732 7285	aat/att	More info
SstI	1	894	gagct/c	More info

FIG. 14-60

The following endonucleases were selected but don't cut this sequence:

AccI, AccIII, AfeI, AflII, Aor51HI, AscI, AspI, AtsI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, EcoO65I, EheI, FseI, HpaI, Kasi, Kpn2I, KspI, Mami, MluI, MroI, MspCI, NarI, NheI, NruI, PacI, Pfl123II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, Sali, SbfI, Sfr303I, SgfI, SgrAI, SmiI, SphI, SrfI, Sse8387I, SstII, SwaI, Tth111I, XbaI, XbaII

FIG. 14-61

SEQUENCE LISTING

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Zhou, Xianbo
Rifkind, Richard A.
Marks, Paul A.

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and Uses Thereof

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2/25

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 165 170 175
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 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
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 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
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 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
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3/25

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Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys	Glu	Lys	Gln	Lys
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Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His	Val	Thr	Leu	Glu
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Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu	Gln	His	Leu	Leu
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4/25

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5/25

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6/25

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 Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg Leu Val Ser Arg
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7/25

Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His Pro Ala Met Asp
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 Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala Tyr Asp Pro Leu
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 Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr Thr His Pro Glu
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 His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln Glu Thr Gly
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 Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
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 Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
 705 710 715 720
 Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly Gly Leu Gly Val
 725 730 735
 Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
 740 745 750
 Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
 755 760 765
 Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
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 Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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 Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
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 Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
 820 825 830
 Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
 835 840 845
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<212> DNA

<213> Homo sapiens

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8/25

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<210> 6

<211> 967

<212> PRT

<213> Homo sapiens

<400> 6

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35     40     45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50     55     60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
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Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
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Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100    105    110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
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Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130    135    140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
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Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180    185    190

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9/25

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Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu		
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Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala		
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Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys		
				420				425					430				
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile		
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Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu		
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Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly		
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				485					490					495			
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu		
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Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met		
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Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg		
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10/25

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Thr	Ile	Val	Lys	Pro	Val	Ala	Lys	Glu	Phe	Asp	Pro	Asp	Met	Val	Leu
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<211> 3367

<212> DNA

<213> Homo sapiens

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11/25

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<210> 8

<211> 835

<212> PRT

<213> Homo sapiens

<400> 8

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35          40          45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100         105         110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115         120         125

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12/25

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Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
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Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
				245					250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
			260					265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
	275						280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
290						295					300				
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315					320
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
				325					330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
			340					345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
	355					360						365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
370						375					380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395					400
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala
				405					410					415	
Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys
			420					425					430		
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile
	435					440						445			
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu
450						455					460				
Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly
465					470					475					480
Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly
				485					490					495	
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu
			500					505					510		
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met
	515					520						525			
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg
530						535					540				
Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg
545					550					555					560
Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His
				565					570					575	
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala
			580					585					590		
Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr
	595					600						605			
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu
610						615						620			

13/25

Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
 820 825 830
 Cys Ile Ala
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 <212> DNA
 <213> Homo sapiens

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 ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
 aagtcagaag ttccctgtggg cctggagccc atctcacctt tagacctaa gacagacctc 240
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 ctctttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc agggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgaga gaacagcagc ttctctctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
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 gatgatttcc cccttcgaaa aactgaatcc tcagttagta gcagttctcc aggtctgtgt 840
 cccagttcac caacaatgg gccaaactgga agtggtactg aaaatgagac ttccggttttg 900
 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaatt tcatgaagat 960
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 agaggtaccc acaaattgcc ccgtcacaga cccctgaacc gaaccagtc tgcacctttg 1380
 cctcagagca cgttgggtca gctgggtcatt caacagcaac accagcaatt cttggagaag 1440
 cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
 ctgaagcaac caggcagtc ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560

14/25

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gatgaagatg ctcagatcca ggaaatggaa tctgggggagc aggctgcttt tatgcaacag 1740
gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

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<210> 10

<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

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 20      25      30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35      40      45
Glu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50      55      60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100      105      110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115      120      125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130      135      140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145      150      155      160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165      170      175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180      185      190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195      200      205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
210      215      220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225      230      235      240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
245      250      255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260      265      270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
275      280      285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
290      295      300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305      310      315      320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
325      330      335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
340      345      350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
355      360      365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
370      375      380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385      390      395      400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

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15/25

405 410 415
 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
 420 425 430
 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
 435 440 445
 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
 450 455 460
 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
 485 490 495
 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
 500 505 510
 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
 515 520 525
 Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
 530 535 540
 Ile Ile
 545

<210> 11
 <211> 590
 <212> PRT
 <213> Homo sapiens

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 Met Met Pro Val Val Asp Pro Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
 210 215 220
 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240
 Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
 245 250 255
 Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
 260 265 270
 Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

16/25

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      275              280              285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
290              295              300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
305              310              315
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
      325              330              335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
      340              345              350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
      355              360              365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
370              375              380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
385              390              395
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
      405              410              415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
      420              425              430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
      435              440              445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
450              455              460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
465              470              475
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
      485              490              495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
500              505              510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
      515              520              525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
530              535              540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
545              550              555
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile
      565              570              575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile
580              585              590

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<210> 12

<211> 1084

<212> PRT

<213> Homo sapiens

<400> 12

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Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro
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Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val
      20              25              30
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro
      35              40              45
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro
50              55              60
Ala Leu Arg Glu Gln Gln Leu Gln Glu Leu Leu Ala Leu Lys Gln
65              70              75              80
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln
      85              90              95
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile
100              105              110
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu

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18/25

610	615	620
Arg Pro Leu Ser Arg	Ala Gln Ser Ser Pro	Ala Ser Ala Thr Phe Pro
625	630	635
Val Ser Val Gln Glu	Pro Thr Lys Pro	Arg Phe Thr Thr Gly Leu
645	650	655
Val Tyr Asp Thr Leu	Met Leu Lys His Gln	Cys Thr Cys Gly Ser Ser
660	665	670
Ser Ser His Pro Glu	His Ala Gly Arg Ile	Gln Ser Ile Trp Ser Arg
675	680	685
Leu Gln Glu Thr Gly	Leu Arg Gly Lys Cys	Glu Cys Ile Arg Gly Arg
690	695	700
Lys Ala Thr Leu Glu	Glu Leu Gln Thr Val	His Ser Glu Ala His Thr
705	710	715
Leu Leu Tyr Gly Thr	Asn Pro Leu Asn Arg	Gln Lys Leu Asp Ser Lys
725	730	735
Lys Leu Leu Gly Ser	Leu Ala Ser Val Phe	Val Arg Leu Pro Cys Gly
740	745	750
Gly Val Gly Val Asp	Ser Asp Thr Ile Trp	Asn Glu Val His Ser Ala
755	760	765
Gly Ala Ala Arg Leu	Ala Val Gly Cys Val	Val Glu Leu Val Phe Lys
770	775	780
Val Ala Thr Gly Glu	Leu Lys Asn Gly Phe	Ala Val Val Arg Pro Pro
785	790	795
Gly His His Ala Glu	Ser Thr Pro Met Gly	Phe Cys Tyr Phe Asn
805	810	815
Ser Val Ala Val Ala	Ala Lys Leu Leu Gln	Gln Arg Leu Ser Val Ser
820	825	830
Lys Ile Leu Ile Val	Asp Trp Asp Val His	His Gly Asn Gly Thr Gln
835	840	845
Gln Ala Phe Tyr Ser	Asp Pro Ser Val Leu	Tyr Met Ser Leu His Arg
850	855	860
Tyr Asp Asp Gly Asn	Phe Phe Pro Gly Ser	Gly Ala Pro Asp Glu Val
865	870	875
Gly Thr Gly Pro Gly	Val Gly Phe Asn Val	Asn Met Ala Phe Thr Gly
885	890	895
Gly Leu Asp Pro Pro	Met Gly Asp Ala Glu	Tyr Leu Ala Ala Phe Arg
900	905	910
Thr Val Val Met Pro	Ile Ala Ser Glu Phe	Ala Pro Asp Val Val Leu
915	920	925
Val Ser Ser Gly Phe	Asp Ala Val Glu Gly	His Pro Thr Pro Leu Gly
930	935	940
Gly Tyr Asn Leu Ser	Ala Arg Cys Phe Gly	Tyr Leu Thr Lys Gln Leu
945	950	955
Met Gly Leu Ala Gly	Gly Arg Ile Val Leu	Ala Leu Glu Gly Gly His
965	970	975
Asp Leu Thr Ala Ile	Cys Asp Ala Ser Glu	Ala Cys Val Ser Ala Leu
980	985	990
Leu Gly Asn Glu Leu	Asp Pro Leu Pro Glu	Lys Val Leu Gln Gln Arg
995	1000	1005
Pro Asn Ala Asn Ala	Val Arg Ser Met Glu	Lys Val Met Glu Ile His
1010	1015	1020
Ser Lys Tyr Trp Arg	Cys Leu Gln Arg Thr	Thr Ser Thr Ala Gly Arg
1025	1030	1035
Ser Leu Ile Glu Ala	Gln Thr Cys Glu Asn	Glu Glu Ala Glu Thr Val
1045	1050	1055
Thr Ala Met Ala Ser	Leu Ser Val Gly Val	Lys Pro Ala Glu Lys Arg
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Pro Asp Glu Glu Pro	Met Glu Glu Pro Pro	Leu
1075	1080	

<210> 13

19/25

<211> 3550

<212> DNA

<213> Homo sapiens

<400> 13

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20/25

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22/25

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24/25

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25/25

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7/25

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 675 680 685
 Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
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8/25

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<212> PRT

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 50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100          105          110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115          120          125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130          135          140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
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Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
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9/25

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 Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
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 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
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 675 680 685

10/25

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11/25

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ctcttaa
3367

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<210> 8
 <211> 835
 <212> PRT
 <213> Homo sapiens

<400> 8
 Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
 1 5 10 15
 Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
 20 25 30
 Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125

12/25

Gly	Lys	Asp	Arg	Gly	Arg	Glu	Arg	Ala	Val	Ala	Ser	Thr	Glu	Val	Lys
130						135					140				
Gln	Lys	Leu	Gln	Glu	Phe	Leu	Leu	Ser	Lys	Ser	Ala	Thr	Lys	Asp	Thr
145					150					155					160
Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
				165					170					175	
Tyr	Thr	Ala	Ala	His	His	Thr	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Leu
				180				185					190		
Ser	Gly	Thr	Ser	Pro	Ser	Tyr	Lys	Tyr	Thr	Leu	Pro	Gly	Ala	Gln	Asp
				195			200					205			
Ala	Lys	Asp	Asp	Phe	Pro	Leu	Arg	Lys	Thr	Glu	Ser	Ser	Val	Ser	Ser
						215					220				
Ser	Ser	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly
225					230					235					240
Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
				245					250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
				260				265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
				275			280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
						295					300				
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315					320
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
				325					330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
				340				345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
				355			360					365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
						375					380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395					400
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala
				405					410					415	
Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys
				420				425					430		
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile
				435			440					445			
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu
				450		455					460				
Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly
465					470					475					480
Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly
				485					490					495	
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu
				500				505					510		
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met
				515			520					525			
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg
						535					540				
Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg
545					550					555					560
Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His
				565					570					575	
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala
				580				585					590		
Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr
				595			600					605			
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu
				610			615					620			

13/25

Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
 820 825 830
 Cys Ile Ala
 835

<210> 9

<211> 1791

<212> DNA

<213> Homo sapiens

<400> 9

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 ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
 aagtcagaag ttctgtgtgg cctggagccc atctcacctt tagacctaa gacagacctc 240
 aggatgatga tgcccggtgt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta 300
 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgagca gaacagcagc ttctctctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
 cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
 ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaa 780
 gatgatttcc ccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggtctgtgt 840
 ccagttcac caaacaatgg gccaaactgga agtggttactg aaaatgagac ttccggtttt 900
 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcatttcta tcatgaagat 960
 tccatgaacc tgctaagtct ttatacctct ccttctttgc ccaacattac cttggggctt 1020
 cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
 acgcagacgc ttaggcaagg tgttcctctg cctgggcagt atggaggcag catcccggca 1140
 tcttcagacc accctcatgt tacttttagag ggaaagccac ccaacagcag ccaccaggct 1200
 ctctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct tgtagctgtg 1260
 ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
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 cctcagagca cgttggctca gctggtcatt caacagcaac accagcaatt cttggagaag 1440
 cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
 ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560

14/25

atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgtttgt 1620
 gtggatgaca cactgggaca agttggggct gtgaagggtca aggaggaacc agtggacagt 1680
 gatgaagatg ctcagatcca ggaaatggaa tctgggggagc aggtgtcttt tatgcaacag 1740
 gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

<210> 10

<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
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 Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
 20 25 30
 Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
 210 215 220
 Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
 225 230 235 240
 Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
 245 250 255
 Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
 260 265 270
 Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
 275 280 285
 Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
 290 295 300
 Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
 305 310 315 320
 Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
 325 330 335
 Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
 340 345 350
 Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
 355 360 365
 Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
 370 375 380
 Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
 385 390 395 400
 Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

15/25

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          405          410          415
Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
          420          425          430
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
          435          440          445
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
          450          455          460
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
465          470          475          480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
          485          490          495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
          500          505          510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
          515          520          525
Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
          530          535          540
Ile Ile
545

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<210> 11

<211> 590

<212> PRT

<213> Homo sapiens

<400> 11

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Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
1          5          10          15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
          20          25          30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
          35          40          45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
          50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
          85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
          100          105          110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
          115          120          125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
          130          135          140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145          150          155          160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
          165          170          175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
          180          185          190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
          195          200          205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
          210          215          220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225          230          235          240
Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
          245          250          255
Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Pro Gly
          260          265          270
Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

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16/25

275	280	285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val		
290	295	300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser		
305	310	315
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala		
325	330	335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys		
340	345	350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr		
355	360	365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu		
370	375	380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu		
385	390	395
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val		
405	410	415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro		
420	425	430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg		
435	440	445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile		
450	455	460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln		
465	470	475
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys		
485	490	495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp		
500	505	510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg		
515	520	525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala		
530	535	540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile		
545	550	555
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile		
565	570	575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile		
580	585	590

<210> 12

<211> 1084

<212> PRT

<213> Homo sapiens

<400> 12

Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro	
1	5
Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val	
20	25
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro	
35	40
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro	
50	55
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln	
65	70
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln	
85	90
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile	
100	105
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu	

17/25

115	120	125
Glu His Gln Arg Lys Leu	Glu Arg His Arg Gln	Glu Gln Glu Leu Glu
130	135	140
Lys Gln His Arg Glu Gln	Lys Leu Gln Gln Leu	Lys Asn Lys Glu Lys
145	150	155
Gly Lys Glu Ser Ala Val	Ala Ser Thr Glu Val	Lys Met Lys Leu Gln
165	170	175
Glu Phe Val Leu Asn Lys	Lys Lys Ala Leu Ala	His Arg Asn Leu Asn
180	185	190
His Cys Ile Ser Ser Asp	Pro Arg Tyr Trp Tyr	Gly Lys Thr Gln His
195	200	205
Ser Ser Leu Asp Gln Ser	Ser Pro Pro Gln Ser	Gly Val Ser Thr Ser
210	215	220
Tyr Asn His Pro Val Leu	Gly Met Tyr Asp Ala	Lys Asp Asp Phe Pro
225	230	235
Leu Arg Lys Thr Ala Ser	Glu Pro Asn Leu Lys	Leu Arg Ser Arg Leu
245	250	255
Lys Gln Lys Val Ala Glu	Arg Arg Ser Ser Pro	Leu Leu Arg Arg Lys
260	265	270
Asp Gly Pro Val Val Thr	Ala Leu Lys Lys Arg	Pro Leu Asp Val Thr
275	280	285
Asp Ser Ala Cys Ser Ser	Ala Pro Gly Ser Gly	Pro Ser Ser Pro Asn
290	295	300
Asn Ser Ser Gly Ser Val	Ser Ala Glu Asn Gly	Ile Ala Pro Ala Val
305	310	315
Pro Ser Ile Pro Ala Glu	Thr Ser Leu Ala His	Arg Leu Val Ala Arg
325	330	335
Glu Gly Ser Ala Ala Pro	Leu Pro Leu Tyr Thr	Ser Pro Ser Leu Pro
340	345	350
Asn Ile Thr Leu Gly Leu	Pro Ala Thr Gly Pro	Ser Ala Gly Thr Ala
355	360	365
Gly Gln Gln Asp Thr Glu	Arg Leu Thr Leu Pro	Ala Leu Gln Gln Arg
370	375	380
Leu Ser Leu Phe Pro Gly	Thr His Leu Thr Pro	Tyr Leu Ser Thr Ser
385	390	395
Pro Leu Glu Arg Asp Gly	Gly Ala Ala His Ser	Pro Leu Leu Gln His
405	410	415
Met Val Leu Leu Glu Gln	Pro Pro Ala Gln Ala	Pro Leu Val Thr Gly
420	425	430
Leu Gly Ala Leu Pro Leu	His Ala Gln Ser Leu	Val Gly Ala Asp Arg
435	440	445
Val Ser Pro Ser Ile His	Lys Leu Arg Gln His	Arg Pro Leu Gly Arg
450	455	460
Thr Gln Ser Ala Pro Leu	Pro Gln Asn Ala Gln	Ala Leu Gln His Leu
465	470	475
Val Ile Gln Gln Gln His	Gln Gln Phe Leu Glu	Lys His Lys Gln Gln
485	490	495
Phe Gln Gln Gln Gln Leu	Gln Met Asn Lys Ile	Ile Pro Lys Pro Ser
500	505	510
Glu Pro Ala Arg Gln Pro	Glu Ser His Pro Glu	Glu Thr Glu Glu Glu
515	520	525
Leu Arg Glu His Gln Ala	Leu Asp Glu Pro Tyr	Leu Asp Arg Leu
530	535	540
Pro Gly Gln Lys Glu Ala	His Ala Gln Ala Gly	Val Gln Val Lys Gln
545	550	555
Glu Pro Ile Glu Ser Asp	Glu Glu Glu Ala Glu	Pro Pro Arg Glu Val
565	570	575
Glu Pro Gly Gln Arg Gln	Pro Ser Glu Gln Glu	Leu Leu Phe Arg Gln
580	585	590
Gln Ala Leu Leu Leu Glu	Gln Gln Arg Ile His	Gln Leu Arg Asn Tyr
595	600	605
Gln Ala Ser Met Glu Ala	Ala Gly Ile Pro Val	Ser Phe Gly Gly His

18/25

610	615	620
Arg Pro Leu Ser Arg	Ala Gln Ser Ser Pro	Ala Ser Ala Thr Phe Pro
625	630	635
Val Ser Val Gln Glu Pro	Pro Thr Lys Pro Arg	Phe Thr Thr Gly Leu
645	650	655
Val Tyr Asp Thr Leu Met	Leu Lys His Gln Cys	Thr Cys Gly Ser Ser
660	665	670
Ser Ser His Pro Glu His	Ala Gly Arg Ile Gln	Ser Ile Trp Ser Arg
675	680	685
Leu Gln Glu Thr Gly Leu	Arg Gly Lys Cys Glu	Cys Ile Arg Gly Arg
690	695	700
Lys Ala Thr Leu Glu Glu	Leu Gln Thr Val His	Ser Glu Ala His Thr
705	710	715
Leu Leu Tyr Gly Thr Asn	Pro Leu Asn Arg Gln	Lys Leu Asp Ser Lys
725	730	735
Lys Leu Leu Gly Ser Leu	Ala Ser Val Phe Val	Arg Leu Pro Cys Gly
740	745	750
Gly Val Gly Val Asp Ser	Asp Thr Ile Trp Asn	Glu Val His Ser Ala
755	760	765
Gly Ala Ala Arg Leu Ala	Val Gly Cys Val Val	Glu Leu Val Phe Lys
770	775	780
Val Ala Thr Gly Glu Leu	Lys Asn Gly Phe Ala	Val Val Arg Pro Pro
785	790	795
Gly His His Ala Glu Glu	Ser Thr Pro Met Gly	Phe Cys Tyr Phe Asn
805	810	815
Ser Val Ala Val Ala Ala	Lys Leu Leu Gln Gln	Arg Leu Ser Val Ser
820	825	830
Lys Ile Leu Ile Val Asp	Trp Asp Val His His	Gly Asn Gly Thr Gln
835	840	845
Gln Ala Phe Tyr Ser Asp	Pro Ser Val Leu Tyr	Met Ser Leu His Arg
850	855	860
Tyr Asp Asp Gly Asn Phe	Pro Gly Ser Gly Ala	Pro Asp Glu Val
865	870	875
Gly Thr Gly Pro Gly Val	Gly Phe Asn Val Asn	Met Ala Phe Thr Gly
885	890	895
Gly Leu Asp Pro Pro Met	Gly Asp Ala Glu Tyr	Leu Ala Ala Phe Arg
900	905	910
Thr Val Val Met Pro Ile	Ala Ser Glu Phe Ala	Pro Asp Val Val Leu
915	920	925
Val Ser Ser Gly Phe Asp	Ala Val Glu Gly His	Pro Thr Pro Leu Gly
930	935	940
Gly Tyr Asn Leu Ser Ala	Arg Cys Phe Gly Tyr	Leu Thr Lys Gln Leu
945	950	955
Met Gly Leu Ala Gly Gly	Arg Ile Val Leu Ala	Leu Glu Gly Gly His
965	970	975
Asp Leu Thr Ala Ile Cys	Asp Ala Ser Glu Ala	Cys Val Ser Ala Leu
980	985	990
Leu Gly Asn Glu Leu Asp	Pro Leu Pro Glu Lys	Val Leu Gln Gln Arg
995	1000	1005
Pro Asn Ala Asn Ala Val	Arg Ser Met Glu Lys	Val Met Glu Ile His
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19/25

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20/25

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22/25

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24/25

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MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19051-

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12N 9/78, 9/00, 9/14, 1/20, 15/00; C07H 21/04 US CL : 435/227, 183, 195, 252.3, 320.1; 536/23.2 According to International Patent Classification (IPC) or to both national classification and IPC																										
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/227, 183, 195, 252.3, 320.1; 536/23.2 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN AND WEST. Sequence search in Swissprot, EST, N-GeneSeq, PIR_71, SPTREMBL & issued US patents.																										
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ ID NO : 1, claim 4 (g).</td> <td>4</td> </tr> <tr> <td>A, P</td> <td>ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.</td> <td>1-9, 29</td> </tr> <tr> <td>A</td> <td>WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.</td> <td>1-9, 29</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ ID NO : 1, claim 4 (g).	4	A, P	ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.	1-9, 29	A	WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.	1-9, 29												
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<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																										
<table border="1"> <thead> <tr> <th colspan="2">Special categories of cited documents:</th> <th colspan="2"></th> </tr> </thead> <tbody> <tr> <td>"A"</td> <td>document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T"</td> <td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"B"</td> <td>earlier application or patent published on or after the international filing date</td> <td>"X"</td> <td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L"</td> <td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y"</td> <td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O"</td> <td>document referring to an oral disclosure, use, exhibition or other means</td> <td>"Z"</td> <td>document member of the same patent family</td> </tr> <tr> <td>"P"</td> <td>document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </tbody> </table>			Special categories of cited documents:				"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"B"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O"	document referring to an oral disclosure, use, exhibition or other means	"Z"	document member of the same patent family	"P"	document published prior to the international filing date but later than the priority date claimed		
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"P"	document published prior to the international filing date but later than the priority date claimed																									
Date of the actual completion of the international search 30 October 2002 (30.10.2002)		Date of mailing of the international search report 13 MAR 2003																								
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Tekchand Saidha Telephone No. (703) 308-0196																								

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/190 51

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 & 29 (SEQ ID NOS : 1 & 2)

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19051

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, 29, drawn to isolated nucleic acid, the encoded protein and protein composition.

Group II, claim(s) 10, drawn to antibody.

Group III, claim(s) 11-13, drawn to a method of identifying a compound - modulate DNA expression.

Group IV, claim(s) 14-19, 33, drawn to a method of identifying a compound that modulate enzymatic activity.

Group V, claim(s) 20-25, 34, drawn to a method of identifying a compound that modulate transcriptional repression activity of the polypeptide.

Group VI, claim(s) 26-27, drawn to a method of identifying a compound that modulate expression of a nucleic acid molecule.

Group VII, claim(s) 28, drawn to a method of identifying a polypeptide that interacts with a polypeptide of claim 1 in a two-hybrid system.

Group VIII, claim(s) 30-32, drawn to a method of diagnosing a cell proliferation disease.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. SEQ ID NO : 1 and 2 [HDAC9].
2. SEQ ID NO : 3 and 4 [HDAC9a].
3. SEQ ID NO : 5 and 6 [HDAC9- Δ NLS].
4. SEQ ID NO : 7 and 8 [HDAC9a- Δ NLS].
5. SEQ ID NO : 9 and 10 [HDRP- Δ NLS].

The claims are deemed to correspond to the species listed above in the following manner:

Each of the claims listed in groups I-VIII correspond to each of the 5 species which are structurally distinct.

The following claim(s) are generic: 1-5.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has a special technical feature of the nucleotide sequence encoding a specific histone deacetylase which Groups II-VIII do not share; Group II has a special technical feature of the antibody to a specific histone deacetylase which Groups I & III-VIII do not share; Groups III-VIII employ nucleic acid or polypeptide in various method of identifying compounds or polypeptides for distinct uses. Further, in view of 37 CFR 1.475 (b), when claims corresponding to different categories of inventions are present then only (3) applies and additional methods of use are deemed to lack unity.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The various species correspond to nucleic acid and polypeptide sequences which are structurally and in activity distinct from each other, therefore lack the same or corresponding special technical feature.